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(54) POLYPEPTIDE, cDNA ENCODING THE POLYPEPTIDE, AND USE OF THE BOTH

(57) A novel polypeptide obtained from a human library by the SST technique; a process for producing the polypeptide; a cDNA encoding the polypeptide; a fragment selectively hybridizing with the sequence of the cDNA; a replication or expression plasmid having the cDNA integrated thereinto; a host cell transformed with the plasmid; an antibody against the polypeptide; and a pharmaceutical composition containing the polypeptide or the antibody.

EP 1 022 286 A1

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Description

Technical Field

[0001] The present invention relates to novel polypeptides, a method for preparation of them, a cDNA encoding it, a vector containing it, a host cell transformed with the vector, an antibody against the peptide, and a pharmaceutical composition containing the polypeptide or the antibody.

Technical Background

[0002] Until now, when a man skilled in the art intends to obtain a particular polypeptide or a cDNA encoding it, he generally utilizes methods by confirming an aimed biological activity in a tissue or in a cell medium, isolating and purifying the polypeptide and then cloning a gene or methods by "expression-cloning" with the guidance of the said biological activity. However, physiologically active polypeptides in living body have often many kinds of activities. Therefore, it happens increasingly that after cloning a gene, the isolated gene is found to be identical to that encoding a polypeptide already known. In addition, some factors could be generated in only a very slight amount and/or under specific conditions and it makes difficult to isolate and to purity the factor and to confirm its biological activity.

[0003] Recent rapid developments in techniques for constructing cDNAs and sequencing techniques have made it possible to quickly sequence a large amount of cDNAs. By utilizing these techniques, a process, which comprises constructing cDNAs library using various cells or tissues, cloning the cDNA at random, identifying the nucleotide sequences thereof, expressing novel polypeptides encoded by them, is now in progress. Although this process is advantageous in that a gene can be cloned and information regarding its nucleotide sequence can be obtained without any biochemical or genetic analysis, the target gene can be discovered thereby only accidentally in many cases.

[0004] The present inventors have studied cloning method to isolate genes encoding proliferation and/or differentiation factors functioning in hematopoietic systems and immune systems. Focusing their attention on the fact that most of the secretory proteins such as proliferation and/or differentiation factors (for example various cytokines) and membrane proteins such as receptors thereof (hereafter these proteins will be referred to generally as secretory proteins and the like) have sequences called signal peptides in the N-termini, the inventors have conducted extensive studies on a process for efficiently and selectively cloning a gene encoding for a signal peptide. Finally, we have successfully developed a screening method for the signal peptides (signal sequence trap (SST)) by using mammalian cells (See Japanese Patent Application No. Hei 6-13951). We also developed yeast SST method on the same concept By the method based on the same conception using yeast (yeast SST method), genes including sequence encoding signal peptide can be identified more easily and efficiently (See USP No. 5,536, 637).

Disclosure of the present invention

[0005] The present inventors et al. have diligently performed certain investigation in order to isolate novel factors (polypeptides) useful for treatment, diagnosis and/or study, particularly, secretory proteins containing secretory signal and membrane protein.

[0006] From the result, the present inventors achieved to find novel secretory proteins and membrane proteins produced from cell lines and tissue, for example, human placenta, human adult brain tissue, cell lines derived from human brain tissue, human bone, cell line derived from human bone marrow, and endothelial cell line of vein derived from human umbilical cord and cDNAs encoding them, and then completed the present invention.

[0007] The present invention provides the cDNA sequences identified as done ON056, ON034, OX003 which were isolated by the said yeast SST method using cDNA libraries prepared from human placenta tissue. Clone ON056, ON034, OX003 were full-length cDNA including full cDNA sequences encoding secretory proteins (Each protein is represented as ON056, ON034, OX003 protein, respectively).

[0008] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of ON056, ON034, OX003 of the present invention. From the above, it was proved that polypeptides of the present invention were new secretary proteins.

[0009] The present invention provides the cDNA sequences identified as clone OA052, OC004, OM017, OM101, OM126, OM160, OMA016a, OMA016b, OMB130, OMB142, OVB100 which were isolated by the said yeast SST method using cDNA libraries prepared from human adult brain tissue and cell lines derived from human brain tissue (T98G, IMR-32, and CCF-STTG1). Clone OA052, OC004, OM017, OM101, OM126, OM160, OMA016a, OMA016b, OMB130, OMB142, OVB100003 were full-length cDNA including full cDNA sequences encoding secretory protein (Each protein is represented as OA052, OC004, OM017, OM101, OM126, OM160, OMA016a, OMA016b, OMB130,

OMB142, OVB100 protein, respectively).

[0010] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OA052, OC004, OM017, OM101, OM126, OM160, OMA016a, OMA016b, OMB130, OMB142, OVB100 of the present invention. From these results, it was proved that polypeptides of the present invention were new secretary proteins.

[0011] The present invention provides the cDNA sequences identified as done OAF062, OAF075, OAG119 which were isolated by the said yeast SST method using cDNA libraries prepared from human bone and bone marrow cell line (HAS303, LP101. Clone OAF062, OAF075, OAG119003 were full-length cDNA including full cDNA sequences encoding secretory protein (Each protein is represented as OAF062, OAF075, OAG119 protein, respectively).

[0012] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAF062, OAF075, OAG119 of the present invention. From these results, it was proved that polypeptides of the present invention were new secretary proteins.

[0013] The present invention provides the cDNA sequences identified as clone OAH040, OAH058 which were isolated by the said yeast SST method using cDNA libraries prepared from epithelial cell line of human umbilical vein (HUV-EC-C) . Clone OAH040, OAH058003 were full-length cDNA including full cDNA sequences encoding secretory protein (Each protein is represented as OAH040, OAH058 protein, respectively).

[0014] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAH040, OAH058 of the present invention. From these results, it was proved that polypeptides of the present invention were new secretary proteins.

[0015] The present invention provides the cDNA sequences identified as clone OM011, OM028, OMB092, OMB108, OT007 which were isolated by the said yeast SST method using cDNA libraries prepared from human adult brain tissue and cell lines derived from human brain tissue (IMR-32) . Clone OM011, OM028, OMB092, OMB108,

OT007は

membrane protein (Each protein is represented as OM011, OM028, OMB092, OMB108, OT007 protein, respectively).

[0016] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OM011, OM028, OMB092, OMB108, OT007 of the present invention. From these results, it was proved that polypeptides of the present invention were new secretary proteins.

[0017] The present invention provides the cDNA sequences identified as clone OAG051, OUB068 which were isolated by the said yeast SST method using cDNA libraries prepared from human bone and bone marrow cell line (LP101 and U-2OS). Clone OAG051,

OUB068は

membrane protein (Each protein is represented as OAG051, OUB068 protein, respectively).

[0018] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAG051, OUB068 of the present invention. From these results, it was proved that polypeptides of the present invention were new secretary proteins.

[0019] That is to say, the present invention relates to

(1) a polypeptide comprising an amino acid sequence of SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79,

(2) a cDNA encoding the polypeptide described in (1),

(3) a cDNA comprising a nucleotide sequence of SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77 or 80, and

(4) a cDNA comprising a nucleotide sequence of SEQ ID NOS. 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42,

45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81.

Brief Description of the Drawing

[0020]

Fig. 1 is a printed data of electrophoresis (SDS-PAGE). Each prepared fraction and the solubilized fraction obtained from insolble fraction by urea described in Example 1 were subjected to SDS-PAGE. The proteins on the gel were detected by image analyzer (BAS2000) as shown in the Fig. 1. The expression of ON056 in E. coli is shown at the arrowhead in the figure.

Detailed Description of the present invention

[0021] The present invention relates to a substantially purified form of the polypeptide comprising the amino acid sequence shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79, homologue thereof, fragment thereof or homologue of the fragment.

[0022] Further, the present invention relates to cDNAs encoding the above peptides. More particularly the invention is provided cDNAs comprising nucleotide sequence shown in SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77, 80, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81, and cDNA containing a fragment which is selectively hybridizing to the cDNA comprising nucleotide sequence shown in SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77, 80, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 46, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81. A said cDNA capable for hybridizing to the cDNA includes the contemporary sequence of the above sequence.

[0023] A polypeptide comprising amino add sequence shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79 in substantially purified form will generally comprise the polypeptide in a preparation in which more than 90%, e.g. 95%, 98% or 99% of the polypeptide in the preparation is that of the SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79.

[0024] A homologue of polypeptide comprising amino add sequence shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79 will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% homologous to the polypeptide comprising the said amino add sequence over a region of at least 20, preferably at least 30, for instance 40, 60 or 100 more contiguous amino acids. Such a polypeptide homologue will be referred to a polypeptide of the present invention.

[0025] Generally, a fragment of polypeptide comprising amino acid sequence shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79 or its homologues will be at least 10, preferably at least 15, for example 20, 25, 30, 40, 50 or 60 amino acids in length.

[0026] A cDNA capable of selectively hybridizing to the cDNA comprising nucleotide sequence shown in SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77, 80, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81 will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% homologous to the cDNA comprising the said nucleotide sequence over a region of at least 20, preferably at least 30, for instance 40, 60 or 100 or more contiguous nucleotides. Such a cDNA will be referred to "a cDNA of the present invention".

[0027] Fragments of the cDNA comprising nucleotide sequence shown in SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77, 80, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81 will be at least 10, preferably at least 15, for example 20, 25, 30 or 40 nucleotides in length, and will be also referred to "a cDNA of the present invention" as used herein.

[0028] A further embodiment of the present invention provides replication and expression vectors carrying cDNA of the present invention. The vectors may be, for example, plasmid, virus or phage vectors provided with an origin of replication, optionally a promoter for the expression of the said cDNA and optionally a regulator of the promoter. The vector may contain one or more selectable marker genes, for example ampicillin resistance gene. The vector may be used in vitro, for example of the production of RNA corresponding to the cDNA, or used to transfect a host cell.

[0029] A further embodiment of the present invention provides host cells transformed, with the vectors for the replication and expression of the cDNA of the present invention, including the cDNA comprising nucleotide sequence shown in SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77, 80, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81 or the open reading frame thereof. The cells will be chosen to be compatible with the vector and may for example be bacterial, yeast, insect cells or mammalian cells.

[0030] A further embodiment of the present invention provides a method of producing a polypeptide which comprises culturing host cells of the present invention under conditions effective to express a polypeptide of the present invention. Preferably, in addition, such a method is carried out under conditions in which the polypeptide of the present invention is expressed and then produced from the host cells.

[0031] cDNA of the present invention may also be inserted into the vectors described above in an antisense orientation in order to prove for the production of antisense RNA. Such antisense RNA may be used in a method of controlling the levels of a polypeptide of the present invention in a cell.

[0032] The invention also provides monoclonal or polyclonal antibodies against a polypeptide of the present invention. The invention further provides a process for the production of monoclonal or polyclonal antibodies to the polypeptides of the present invention. Monoclonal antibodies may be prepared by common hybridoma technology using polypeptides of the present invention or fragments thereof, as an immunogen. Polyclonal antibodies may also be prepared by common means which comprise inoculating host animals, (for example a rat or a rabbit etc.), with polypeptides of the present invention and recovering immune serum.

[0033] The present invention also provides pharmaceutical compositions containing a polypeptide of the present invention, or an antibody thereof, in association with a pharmaceutically acceptable diluent and/or carrier.

[0034] The polypeptide of the present invention specified in (1) includes that which a part of their amino acid sequence is lacking (e.g., a polypeptide comprised of the only essential sequence for revealing a biological activity in an amino add sequence shown in SEQ ID NO. 1), that which a part of their amino acid sequence is replaced by other amino adds (e.g., those replaced by an amino acid having a similar property) and that which other amino acids are added or inserted into a part of their amino acid sequence, as well as those comprising the amino acid sequence shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79.

[0035] As known well, there are one to six kinds of codon as that encoding one amino acid (for example, one kind of codon for Methionine (Met), and six kinds of codon for Leucine (Leu) are known). Accordingly, the nucleotide sequence of cDNA can be changed in order to encode the polypeptide having the same amino acid sequence.

[0036] The cDNA of the present invention, specified in (2) includes a group of every nucleotide sequence encoding polypeptides (1) shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79. There is a probability that yield of a polypeptide is improved by changing a nucleotide sequence.

[0037] The cDNA specified in (3) is the embodiment of the cDNA shown in (2), and indicate the sequence of natural form.

[0038] The cDNA shown in (4) indicates the sequence of the cDNA specified in (3) with natural non-translational region.

[0039] cDNA carrying nucleotide sequence shown in SEQ ID NOS. 3 is prepared by the following method:

[0040] Brief description of Yeast SST method (see USP No. 5, 536, 637) is as follows.

[0041] Yeast such as Saccharomyces cerevisiae should secrete invertase into the medium in order to take sucrose or raffinose as a source of energy or carbon. (Invertase is an enzyme to cleave raffinose into sucrose and melibiose, sucrose into fructose and glucose.). It is known that many known mammalian signal sequence make yeast secrete its invertase. From these knowledge, SST method was developed as a screening method to find novel signal peptide which make it possible can to secrete yeast invertase from mammalian cDNA library. SST method uses yeast growth on raffinose medium as a marker. Non-secretory type invertase gene SUC2 (GENBANK Accession No. V 01311) lacking initiation codon ATG was inserted to yeast expression vector to prepare yeast SST vector pSUC2. In this expression vector, ADH promoter, ADH terminator (both were derived from AAH5 plasmid (Gammerer, Methods in Enzymol. 101, 192-201, 1983)), 2m ori (as a yeast replication origin), TRP1 (as a yeast selective marker), ColE1 ori (as a E. Coli replication origin) and ampicillin resistance gene (as a drug resistance marker) were inserted. Mammalian cDNA was inserted into the upstream of SUC2 gene to prepare yeast SST cDNA library. Yeast lacking secretory type invertase, was transformed with this library. If inserted mammalian cDNA encodes a signal peptide, yeast could survive in raffinose medium as a result of restoring secretion of invertase. Only to culture yeast colonies, prepare plasmids and determine the nucleotide sequence of the insert cDNAs, it is possible to identify novel signal peptide rapidly and easily.

[0042] Preparation of yeast SST cDNA library is as follows:

(1) mRNA is isolated from the targeted cells, double-strand synthesis is performed by using random primer with certain restriction enzyme (enzyme I) recognition site,

(2) obtained double-strand cDNA is ligated to adapter containing certain restriction endonuclease (enzyme II) recognition site, differ from enzyme I, digested with enzyme I and fractionated in a appropriate size,

(3) obtained cDNA fragment is inserted into yeast expression vector on the upstream region of invertase gene which signal peptide is deleted and the library was transformed.

[0043] Detailed description of each step is as follows:

(1) mRNA is isolated from mammalian organs and cell lines stimulate them with appropriate stimulator if necessary) by known methods (Molecular Cloning (Sambrook, J., Fritsch, E. F. and Maniatis, T., Cold Spring Harbor Laboratory Press, 1989) or Current Protocol in Molecular Biology (F. M. Ausubel et al, John Wiley & Sons, Inc.) if not remark especially).

TG98G (human glioblastoma cell line: ATCC No. CRL-1690), IMR-32 (human neuroblastoma cell line: ATCC No. CCL-127), U-2OS (human osteosarcoma cell line: ATCC No. HTB-96), CCF-STTG1 (human astrocytoma cell line: ATCC No. CRL-1718), HAS303 (human bone marrow stroma cell line: provide from Professor Keisuke Sotoyama, Dr. Makoto Aizawa of First Medicine, Tokyo Medical College; see J. Cell. Physiol., 148, 245-251, 1991 and Experimental Hematol., 22, 482-487, 1994), LP101 (human bone marrow stroma cell line: provide from Professor Keisuke Sotoyama, Dr. Makoto Aizawa of First Medicine, Tokyo Medical College; see J. Cell. Physiol., 148, 245-251, 1991 and Experimental Hematol., 22, 482-487, 1994) and HUV-EC-C (endothelial cell of vein derived from human umbilical cord: ATCC No. CRL-1730) are chosen as a cell line. Human placenta and human adult brain are chosen as a tissue source. Double-strand cDNA synthesis using random primer is performed by known methods.

Any sites may be used as restriction endonuclease recognition site I which is linked to adapter and restriction endonuclease recognition site II which is used in step (2), if both sites are different each other. Preferably, XhoI is used as enzyme I and EcoRI as enzyme II.

In step (2), cDNA is created blunt-ends with T4 DNA polymerase, ligated enzyme II adapter and digested with enzyme I. Fragment cDNA is analyzed with agarose-gel electrophoresis (AGE) and is selected cDNA fraction ranging in size from 300 to 800 bp. As mentioned above, any enzyme may be used as enzyme II if it is not same the enzyme I.

In step (3), cDNA fragment obtained in step (2) is inserted into yeast expression vector on the upstream region of invertase gene which signal peptide is deleted. E. Coli was transformed with the expression vector. Many vectors are known as yeast expression plasmid vector. For example, YEp24 is also functioned in E. Coli. Preferably pSUC2 as described above is used.

[0044] Many host E. Coli strains are known for transformation, preferably DH10B competent cell is used. Any known transformation method is available, preferably it is performed by electropolation method. Transformant is cultured by conventional methods to obtain cDNA library for yeast SST method.

[0045] However not every all of the clones do not contain cDNA fragment Further all of the gene fragments do not encode unknown signal peptides. It is therefore necessary to screen a gene fragment encoding for an unknown signal peptide from the library.

[0046] Therefore, screening of fragments containing a sequence encoding an appropriate signal peptide is performed by transformation of the cDNA library into Saccharomyces cerevisiae (e.g. YT455 strain) which lack invertase (it may be prepared by known methods.). Transformation of yeast is performed by known methods, e.g. lithium acetate method. Transformant is cultured in a selective medium, then transferred to a medium containing raffinose as a carbon source. Survival colonies are selected and then prepared plasmid. Survival colonies on a raffinose-medium indicates that some signal peptide of secretory protein was inserted to this done.

[0047] As for isolated positive clones, the nucleotide sequence is determined. As to a cDNA encodes unknown prptein, full-length clone may be isolated by using cDNA fragment as a probe and then determined to obtain full-length nucleotide sequence. These manipulation is performed by known methods.

[0048] Once the nucleotide sequences shown in SEQ ID NO. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77, 80, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81 are determined partially or preferably fully, it is possible to obtain DNA encode mammalian protein itself, homologue or subset. cDNA library or mRNA derived from mammals was screened by PCR with any synthesized oligonucleotide primers or by hybridization with any fragment as a probe. It is possible to obtain DNA encodes other mammalian homologue protein from other mammalian cDNA or genome library.

[0049] If a cDNA obtained above contains a nucleotide sequence of cDNA fragment obtained by SST (or consensus sequence thereof), it will be thought that the cDNA encodes signal peptide. So it is dear that the cDNA will be full-length or almost full. (All signal peptides exist at N-termini of a protein and are encoded at 5'-temini of open reading frame of cDNA.)

[0050] The confirmation may be carried out by Northern analysis with the said cDNA as a probe. It is thought that the cDNA is almost complete length, if length of the cDNA is almost the same length of the mRNA obtained in the hybridizing band.

[0051] Once the nucleotide sequences shown in SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77, 80, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81 are determined, DNAs of the invention are obtained by chemical synthesis, or by hybridization making use of nucleotide fragments which are chemically synthesized as a probe. Furthermore, DNAs of the

invention are obtained in desired amount by transforming a vector that contains the DNA into a proper host, and culturing the transformant.

[0052] The polypeptides of the present invention may be prepared by:

(1) isolating and purifying from an organism or a cultured cell,
(2) chemically synthesizing, or
(3) using recombinant cDNA technology,

preferably, by the method described in (3) in an industrial production.

[0053] Examples of expression system (host-vector system) for producing a polypeptide by using recombinant cDNA technology are the expression systems of bacteria, yeast, insect cells and mammalian cells.

[0054] In the expression of the polypeptide, for example, in E. Coli, the expression vector is prepared by adding the initiation codon (ATG) to 5' end of a cDNA encoding mature peptide, connecting the cDNA thus obtained to the downstream of a proper promoter (e.g., trp promoter, lac promoter, λPL promoter, T7 promoter etc.), and then inserting it into a vector (e.g., pBR322, pUC18, pUC19 etc.) which functions in an E. coli strain.

[0055] Then, an E. coli strain (e.g., E. coli DH1 strain, E. coli JM109 strain, E. coli HB101 strain, etc.) which is transformed with the expression vector described above may be cultured in a appropriate medium to obtain the desired polypeptide. When a signal sequence of bacteria (e.g., signal sequence of pel B) is utilized, the desired polypeptide may be also released in periplasm. Furthermore, a fusion protein with other polypeptide may be also produced readily.

[0056] In the expression of the polypeptide, for example, in a mammalian cells, for example, the expression vector is prepared by inserting the cDNA encoding nucleotide shown in SEQ ID NOS. 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81 into the downstream of a proper promoter (e.g., SV40 promoter, LTR promoter, metallothionein promoter etc.) in a proper vector (e.g., retrovirus vector, papilloma virus vector, vaccinia virus vector, SV40 vector, etc.). A proper mammalian cell (e.g., monkey COS-7 cell, Chinese hamster CHO cell, mouse L cell etc.) is transformed with the expression vector thus obtained, and then the transformant is cultured in a proper medium to express the aimed secretory protein and membrane protein of the present invention by the following method.

[0057] In case of secretory protein as for the present invention, the aimed polypeptide was expressed in the supernatant of the cells. In addition, fusion protein may be prepared by conjugating cDNA fragment encoding the other polypeptide, for example, Fc portion of antibody.

[0058] On the other hand, in case of membrane protein as for the present invention, the aimed polypeptide was expressed on the cell membrane. A cDNA encoding the nucleotide sequence of SEQ ID NOS. 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81 with deletion of extracellular region was inserted into the said vector, transfected into the an adequate mammalian cells to secret the aimed soluble polypeptide in the culture medium. In addition, fusion protein may be prepared by conjugating cDNA fragment encoding the said mutant with deletion of extracellular region and other polypeptide, for example, Fc portion of antibody.

[0059] The polypeptide available by the way described above can be isolated and purified by conventional biochemical method.

Industrial Applicability

[0060] It is considered that the polypeptide of the present invention and a cDNA which encodes the polypeptide will show one or more of the effects or biological activities (including those which relates to the assays cited below) The effects or biological activities described in relation to the polypeptide of the present invention are provided by administration or use of the polypeptide or by administration or use of a cDNA molecule which encodes the polypeptide (e.g., vector suitable for gene therapy or cDNA introduction).

[Cytokine activity and cell proliferation/differentiation activity]

[0061] The protein of the present invention may exhibit cytokine, cell proliferation (either inducing or inhibiting) or cell differentiation (either inducing or inhibiting) activity or may induce production of other cytokines in certain cell populations. Many protein factors discovered to date, including all known cytokines, have exhibited activity in one or more factor dependent cell proliferation assays, and hence the assays serve as a convenient confirmation of cytokine activity. The activity of a polypeptide of the present invention is evidenced by any one of a number of routine factor dependent cell proliferation assays for cell lines.

[Immune stimulating/suppressing activity]

[0062] The protein of the present invention may also exhibit immune stimulating or immune suppressing activity. The protein of the present invention may be useful in the treatment of various immune deficiencies and disorders (inducing severe combined immunodeficiency (SCID)), e.g., in regulating (up or down) growth and proliferation of T and/or B lymphocytes, as well as effecting the cytolytic activity of NK cells and other cell populations. These immune deficiencies may be genetic or be caused by viral infection such as HIV as well as bacterial or fungal infections, or may result from autoimmune disorders. More specifically, infectious diseases causes by viral, bacterial, fungal or other infection may be treatable using the polypeptide of the present invention, including infections by HIV, hepatitis viruses, herpes viruses, mycobacteria, leshmania, malaria and various fungal infections such as candida. Of course, in this regard, the protein of the present invention may also be useful where a boost to the immune system generally would be indicated, i.e., in the treatment of cancer.

[0063] The protein of the present invention may be useful in the treatment of allergic reactions and conditions, such as asthma or other respiratory problems. The protein of the present invention may also be useful in the treatment of the other conditions required to suppress the immuno system (for example, asthma or respiratory disease.)

[0064] The protein of the present invention may also suppress chronic or acute inflammation, such as, for example, that associated with infection such as septic shock or systemic inflammatory response syndrome (SIRS), inflammatory bowel disease, Crohn's disease or resulting from over production of cytokines such as TNF or IL-I wherein the effect was demonstrated by IL-11.

[Hematopoiesis regulating activity]

[0065] The protein of the present invention may be useful in regulation of hematopoiesis and, consequently, in the treatment of myeloid or lymphoid cell deficiencies. Even marginal biological activity in support of colony forming cells or of factor-dependent cell lines indicates involvement in regulating hematopoiesis. The said biological activities are concerned with the following all or some example(s). e.g. in supporting the growth and proliferation of erythroid progenitor cells alone or in combination with other cytokines, thereby indicating utility, for example, in treating various anemia or for use in conjunction with irradiation/chemotherapy to stimulate the production of erythroid precursors and/or erythroid cells; in supporting the growth and proliferation of myeloid cells such as granulocytes and monocytes/macrophages (i.e., traditional CSF activity) useful, for example, in conjunction with chemotherapy to prevent or treat consequent myelo-suppression; in supporting the growth and proliferation of megakaryocytes and consequently of platelets thereby allowing prevention or treatment of various platelet disorders such as thrombocytopenia, and generally for use in place of or complimentary to platelet transfusions; and/or in supporting the growth and proliferation of hematopoietic stem cells which are capable of maturing to any and all of the above-mentioned hematopoietic cells and therefore find therapeutic utility in various stem cell disorders (such as those usually titated with transplantation, including, without limitation, aplastic anemia and paroxysmal nocturnal hemoglobinuria), as well as in repopulating the stem cell compartment post irradiation/chemotherapy, either in-vitro or ex-vivo (i.e. in conjunction with bone marrow transplantation) as normal cells or genetically manipulated for gene therapy.

[0066] The activity of the protein of the present invention may, among other means, be measured by the following methods :

[Tissue generation/regeneration activity]

[0067] The protein of the present invention also may have utility in compositions used for bone, cartilage, tendon, Ligament and/or nerve tissue growth or regeneration, as well as for wound healing and tissue repair, and in the treatment of bums, incisions and ulcers.

[0068] The protein of the present invention, which induces cartilage and/or bone growth in circumstances where bone is not normally formed, may be applied to the healing of bone fractures and cartilage damage or defects in humans and other animals. Such a preparation employing the protein of the present invention may have prophylactic use in dosed as well as open fracture reduction and also in the improved fixation of artificial joints. De novo bone formation induced by an osteogenic agent contributes to the repair of congenital, trauma induced, or oncologic resection induced craniofacial defects, and also is useful in cosmetic plastic surgery.

[0069] The protein of the present invention may also be used in the treatment of periodontal disease, and in other tooth repair processes. Such agents may provide an environment to attract bone-forming cells, stimulate growth of bone-forming cells or induce differentiation of progenitors of bone-forming cells. The protein of the present invention may also be useful in the treatment of osteoporosis or osteoarthritis, such as through stimulation of bone and/or cartilage repair or by blocking inflammation or processes of tissue destruction (collagenase activity, osteodast activity, etc.) mediated by inflammatory processes.

[0070] Another category of tissue regeneration activity that may be attributable to the protein of the present invention is tendon/ligament formation. The protein of the present invention, which induces tendon/ligament-like tissue or other tissue formation in circumstances where such tissue is not normally formed, may be applied to the healing of tendon or ligament tears, deformities and other tendon or ligament defects in humans and other animals. Such a preparation employing the protein inducing a tendon/Ligament-like tissue may have prophylactic use in preventing damage to tendon or ligament tissue, as well as use in the improved fixation of tendon or ligament to bone or other tissues, and in repairing defects to tendon or ligament tissue. De novo tendon/ligament-like tissue formation induced by a composition of the present invention contributes to the repair of congenital, trauma induced, or other tendon or ligament defects of other origin, and is also useful in cosmetic plastic surgery for attachment or repair of tendons or ligaments. The compositions of the present invention may provide an environment to attract tendon- or ligament-forming cells, stimulate growth of tendon- or ligament-forming cells, induce differentiation of progenitors of tendon- or ligament-forming cells, or induce growth of tendon Ligament cells or progenitors ex vivo for return in vivo to effect tissue repair. The compositions of the present invention may also be useful in the treatment of tendinitis, Carnal tunnel syndrome and other tendon or ligament defects. The compositions may also include an appropriate matrix and/or sequestering agent as a carrier as is well known in the art.

[0071] The protein of the present invention may also be useful for proliferation of neural cells and for regeneration of nerve and brain tissue. i.e. for the treatment of central and peripheral nervous system diseases and neuropathies. as well as mechanical and traumatic disorders, which involve degeneration, death or trauma to neural cells or nerve tissue. More specifically, the protein of the présent invention may be used in the treatment of diseases of the peripheral nervous system, such as peripheral nerve injuries, peripheral neuropathy and localized neuropathies, and central nervous system diseases, such as Alzheimer's, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome. Further conditions which may be treated in accordance with the invention include mechanical and traumatic disorders, such as spinal cord disorders, head trauma and cerebrovascular diseases such as stroke. Peripheral neuropathies resulting from chemotherapy or other medical therapies may also be treatable using the polypeptide of the present invention.

[0072] It is expected that the protein of the present invention may also exhibit activity for generation of other tissues, such as organs (including, for example, pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac) and vascular (including vascular endothelium) tissue, or for promoting the proliferation of cells comprising such tissues. Part of the desired effects may be by inhibition of fibrotic scarring to allow normal tissue to regenerate.

[0073] The protein of the present invention may also be useful for gut protection or regeneration and treatment of lung or liver fibrosis, reperfusion injury in various tissues, and conditions resulting from systemic cytokine damage.

[Activin/Inhibin activity]

[0074] The protein of the present invention may also exhibit activin- or inhibin-related activities. Inhibins are characterized by their ability to inhibit the release of follicle stimulating hormone (FSH), while activins are characterized by their ability to stimulate the release of follicle stimulating hormone (FSH). Thus, the protein of the present invention alone or in heterodimers with a member of the inhibin *a family, may be useful as a contraceptive based on the ability of inhibins to decrease fertility in female mammals and decrease spermatogenesis in male mammals. Administration of sufficient amounts of other inhibins can induce infertility in these mammals.
Alternatively, the protein of the present invention, as a homodimer or as a heterodimer with other protein subunits of the inhibin-*b group, may be useful as a fertility inducing therapeutic, based upon the ability of activin molecules in stimulating FSH release from cells of the anterior pituitary (See USP 4,798,885). The protein of the present invention may also be useful for advancement of the onset of fertility in sexually immature mammals, so as to increase the lifetime reproductive performance of domestic animals such as cows, sheep and pigs.

[Chemotactic/chemokinetic activity]

[0075] The protein of the present invention may have chemotactic or chemokinetic activity e.g., functioning as a chemokine, for mammalian cells, including, for example, monocytes, neutrophils, T-cells, mast cells, eosinophils and/or endothelial cells. Chemotactic and chemokinetic proteins can be used to mobilize or attract a desired cell population to a desired site of action. Chemotactic or chemokinetic proteins provide particular advantages in treatment of wounds and other trauma to tissues, as well as in treatment of localized infections. For example, attraction of lymphocytes, monocytes or neutrophils to tumors or sites of infection may result in improved immune responses against the tumor or infecting agent.

[0076] If a protein or peptide can stimulate, directly or indirectly, the directed orientation or movement of such cell population, it has chemotactic activity for a particular cell population. Preferably, the protein or peptide has the ability to directly stimulate directed movement of cells. Whether a particular protein has chemotactic activity for a population of

cells can be readily determined by employing such protein or peptide in any known assay for cell chemotaxis.

[Hemostatic and thrombolytic activity]

[0077] The protein of the present invention may also exhibit hemostatic or thrombolyic activity. As a result, such a protein is expected to be useful in treatment of various coagulation disorders (including hereditary disorders, such as hemophilias) or to enhance coagulation and other hemostatic events in treating wounds resulting from trauma, surgery or other causes. A protein of the present invention may also be useful for dissolving or inhibiting formation of thromboses and for treatment and prevention of conditions resulting therefrom such as, for example, infarction or stroke.

[Receptor/ligand activity]

[0078] The protein of the present invention may also demonstrate activity as receptors, receptor ligands or inhibitors or agonists of receptor/ligand interactions. Examples of such receptors and ligands include, without limitation, cytokine receptors and their ligands, receptor kinases and their ligands, receptor phosphatases and their ligands, receptors involved in cell-cell interactions and their ligands (including cellular adhesion molecules such as Selectins, Integrins and their ligands) and receptor/ligand pairs involved in antigen presentation, antigen recognition and development of cellular and humoral immune responses. Receptors and ligands are also useful for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. The protein of the present invention (including, without limitation, fragments of receptors and ligands) may themselves be useful as inhibitors of receptor/ligand interactions.

[Other activity]

[0079] The protein of the present invention may also exhibit one or more of the following additional activities or effects: inhibiting growth of or killing the infecting agents including bacteria, viruses, fungi and other parasites; effecting (suppressing or enhancing) body characteristics including height, weight, hair color, eye color, skin, other tissue pigmentation, or organ or body part size or shape such as, for example, breast augmentation or diminution etc.; effecting elimination of dietary fat, protein, carbohydrate; effecting behavioral characteristics including appetite, libido, stress, cognition (including cognitive disorders), depression and violent behaviors; providing analgesic effects or other pain reducing effects; promoting differentiation and growth of embryonic stem cells in lineages other than hematopoietic lineages; in the case of enzymes, correcting deficiencies of the enzyme and treating deficiency-related diseases.

[0080] The protein with above activities, is suspected to have following functions by itself or interaction with its ligands or receptors or association with other molecules. For example, proliferation or cell death of B cells, T cells and/or mast cells; specific induction by promotion of class switch of immunoglobulin genes; differentiation of B cells to antibody-forming cells; proliferation, differentiation, or cell death of precursors of granulocytes; proliferation, differentiation, or cell death of precursors of monocytes-macrophages; proliferation, of up regulation or cell death of neutrophils, monocytes-macrophages, eosinophils and/or basophils; proliferation, or cell death of precursors of megakaryocytes; proliferation, differentiation, or cell death of precursors of neutrophils; proliferation, differentiation, or cell death of precursors of T cells and B cells; promotion of production of erythrocytes; sustainment of proliferation of erythrocytes, neutrophils, eosinophils, basophils, monocytes-macrophages, mast cells, precursors of megakaryocyte; promotion of migration of neutrophils, monocytes-macrophages, B cells and/or T cells; proliferation or cell death of thymocytes; suppression of differentiation of adipocytes; proliferation or cell death of natural killer cells; proliferation or cell death of hematopoietic stem cells; suppression of proliferation of stem cells and each hematopoietic precursor cells; promotion of differentiation from mesenchymal stem cells to osteoblasts or chondrocytes, proliferation or cell death of mesenchymal stem cells, osteoblasts or chondrocytes and promotion of bone absorption by activation of osteoclasts and promotion of differentiation from monocytes to osteoclasts.

[0081] The polypeptide of the present invention is also suspected to function to nervous system, so expected to have functions below; differentiation to kinds of neurotransmitter-responsive neurons, survival or cell death of these cells; promotion of proliferation or cell death of glial cells; spread of neural dendrites; survival or cell death of gangriocytes; proliferation, promotion of differentiation, or cell death of astrocytes; proliferation, survival or cell death of peripheral neurons; proliferation or cell death of Schwann cells; proliferation, survival or cell death of motoneurons.

[0082] Furthermore, in the process of development of early embryonic, the polypeptide of the present invention is expected to promote or inhibit the organogenesis of epidermis, brain, backbone, and nervous system by induction of ectoderm, that of notochord connective tissues (bone, muscle, tendon), hemocytes, heart, kidney, and genital organs by induction of mesoderm, and that of digestive apparatus (stomach, intestine, liver, pancreas), respiratory apparatus (lung, trachea) by induction of endoderm. In adult, also, this polypeptide is thought to proliferate or inhibit the above organs.

[0083] Therefore, the polypeptide of the present invention itself is expected to be used as an agent for the prevention or treatment of disease of progression or suppression of immune, nervous, or bone metabolic function, hypoplasia or overgrowth of hematopoletic cells: for example, inflammatory disease (rheumatism, ulcerative colitis, etc.), decrease of hematopoietic stem cells after bone marrow transplantation, decrease of leukocytes, platelets, B-cells, or T-cells after radiation exposure or chemotherapeutic dosage against cancer or leukemia, anemia, infectious disease, cancer, leukemia, AIDS, bone metabolic disease (osteoporosis etc.), various degenerative disease (Alzheimer's disease, multiple sclerosis, etc.), or nervous lesion.

[0084] In addition, since the polypeptide of the present invention is thought to induce the differentiation or growth of organs derived from ectoderm, mesoderm, and endoderm, this polypeptide is expected to be an agent for tissue repair (epidermis, bone, muscle, tendon, heart, kidney, stomach, intestine, liver, pancreas, lung, and trachea, etc.).

[0085] By using polyclonal or monoclonal antibodies against the polypeptide of the present invention, quantitation of the said polypeptide in the body can be performed. It can be used in the study of relationship between this polypeptide and disease or diagnosis of disease, and so on. Polyclonal and monoclonal antibodies can be prepared using this polypeptide or its fragment as an antigen by conventional methods.

[0086] Identification, purification or molecular cloning of known or unknown proteins which bind the polypeptide of the present invention (preferably polypeptide of extracellular domain) can be performed using the polypeptide of the present invention by, for example, preparation of the affinity-column.

[0087] Identification of the downstream signal transmission molecules which interact with the polypeptide of the present invention in cytoplasma and molecular cloning of the gene can be performed by west-western method using the polypeptide of the present invention (preferably polypeptide of transmembrane region or intracellular domain), or by yeast two-hybrid system using the cDNA (preferably cDNA encoding transmembrane region or cytoplasmic domain of the polypeptide).

[0088] Agonists/antagonists of this receptor polypeptide and inhibitors between receptor and signal transduction molecules can be screened using the polypeptide of the present invention.

[0089] cDNAs of the present invention are useful not only the important and essential template for the production of the polypeptide of the present invention which is expected to be largely useful, but also be useful for diagnosis or therapy (for example, treatment of gene lacking, treatment to stop the expression of the polypeptide by antisense cDNA (mRNA)). Genomic cDNA may be isolated with the cDNA of the present invention, as a probe. As the same manner, a human gene encoding which can be highly homologous to the cDNA of the present invention, that is, which encodes a polypeptide highly homologous to the polypeptide of the present invention and a gene of animals excluding mouse which can be highly homologous to the cDNA of the present invention, also may be isolated.

[Application to Medicaments]

[0090] The polypeptide of the present invention or the antibody specific for the polypeptide of the present invention is administered systemically or topically and in general orally or parenterally, preferably parenterally, intravenously and intraventricularly, for preventing or treating the said diseases.

[0091] The doses to be administered depend upon age, body weight, symptom, desired therapeutic effect, route of administration, and duration of the treatment etc. In human adults, one dose per person is generally between 100 μg and 100 mg, by oral administration, up to several times per day, and between 10 μg and 100 mg, by parental administration up to several times per day.

[0092] As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

[0093] The compounds of the present invention, may be administered as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parental administration.

[0094] Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules include soft or hard capsules.

[0095] In such compositions, one or more of the active compound(s) is or are admixed with at least one inert diluent (such as lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate, etc.). The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (such as magnesium stearate etc.), disintegrating agents (such as cellulose calcium glycolate, etc.), stabilizing agents (such as human serum albumin, lactose etc.), and assisting agents for dissolving (such as arginine, asparaginic add etc.).

[0096] The tablets or pills may, if desired, be coated with a film of gastric or enteric materials (such as sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate, etc.), or be coated with more than two films. And then, coating may include containment within capsules of absorbable materials such as gelatin.

[0097] Liquid compositions for oral administration include pharmaceutically-acceptable emulsions, solutions, syrups and elixirs. In such compositions, one or more of the active compound(s) is or are contained in inert diluent(s) com-

monly used (purified water, ethanol etc.). Besides inert diluents, such compositions may also comprise adjuvants (such as wetting agents, suspending agents, etc.), sweetening agents, flavoring agents, perfuming agents, and preserving agents.

[0098] Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s). Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfite etc.), isotonic buffer (sodium chloride, sodium citrate, citric acid, etc.). For preparation of such spray compositions, for example, the method described in the United States Patent No. 2,868,691 or 3,095,355 (herein incorporated in their entireties by reference) may be used.

[0099] Injections for parental administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one or more active compound(s) is or are admixed with at least one inert aqueous diluent(s) (distilled water for injection, physiological salt solution, etc.) or inert non-aqueous diluents(s)(propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSOLBATE 80 (Trade mark) etc.).

[0100] Injections may comprise additional compound other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (such as human serum albumin, lactose, etc.), and assisting agents such as assisting agents for dissolving (arginine, asparaginic acid, etc.).

Best Mode carrying out the Invention

[0101] The invention is illustrated by the following examples, but not limit the invention.

Example 1: Clone ON056

(1) Preparation of Poly(A)$^+$RNA

[0102] Total RNA was prepared from human placenta tissue by TRIzol reagent (Trade Mark, marketed by GIBCO BRL Co.). Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit (Trade name, marketed by Pharmacia Co.).

(2) Preparation of yeast SST cDNA library

[0103] Double strand cDNA was synthesized by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning (Trade name, marketed by GIBCO BRL Co.) with above poly(A)$^+$RNA as template and random 9mer as primer which was containing XhoI site:

5'-CGA TTG AAT TCT AGA CCT GCC TCG AGN NNN NNN NN-3' (SEQ ID NO. 82).

cDNA was ligated EcoRI adapter by DNA ligation kit ver. 2 (Trade name, marketed by Takara Shuzo Co.; this kit was used in all ligating steps hereafter.) and digested by XhoI. cDNAs were separated by agarose-gel electrophoresis. 300~800 bp cDNAs were isolated and were ligated to EcoRI/NotI site of pSUC2 (see US Patent No. 5, 536, 637). E. Coli DH10B strains were transformed by pSUC2 with electropolation to obtain yeast SST cDNA library.

(3) Screening by SST method and determination of nucleotide sequence of SST positive clone

[0104] Plasmids of the said cDNA library were prepared. Yeast YTK12 strains were transformed by the plasmids with lithium acetate method (Current Protocols In Molecular Biology 13.7.1). The transformed yeast were plated on tryptphan-free medium (CMD-Trp medium) for selection. The plate was incubated for 48 hour at 30°C. Replica of the colony (transformant) which was obtained by Accutran Replica Plater (Trade name, marketed by Schleicher & Schuell) were placed onto YPR plate containing raffinose for carbon source, and the plate was incubated for 14 days at 30°C. After 3 days, each colony appeared was streaked on YPR plate again. The plates were incubated for 48 hours at 30°C. Single colony was inoculated to YPD medium and was incubated for 48 hours at 30°C. Then plasmids were prepared. Insert cDNA was amplified by PCR with two kind primers which exist end side of cloning site on pSUC2 (sense strand primers were biotinylated). Biotinylated single strand of cDNAs were purified with Dynabeads (Trade name, marketed by DYNAL Co.) and the nucleotide sequences were determined. Sequencing was performed by Dye Terminator Cycle Sequencing Ready Reaction with DNA Sequencing kit (Trade name, marketed by Applied Biosystems Inc.) and sequence was determined by DNA sequencer 373 (Applied Biosystems Inc.) (All sequencing hereafter was carried out with this method.).

[0105] We tried to carry out cloning of full-length cDNA which was proved to be new one according to the homology search for the obtained nucleotide sequences and deduced amino add sequences in data base. We also confirmed that each cDNA contains signal peptide in view of function and structure, by comparison with known peptide which has signal peptide and deduced amino acid sequence.

(4) Cloning of a full-length cDNA and determination of nucleotide sequence

[0106] A full-length cDNA was cloned using GENETRAPPER cDNA Positive Selection System (marketed by GIBCO BRL Co.). First, dT-primed cDNA library was prepared from poly (A)$^+$RNA in human placenta tissue using pSPORT1 plasmid (marketed by GIBCO BRL Co.), as a vector, by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning. Next, after preparing biotinylated primer ON056-F1 (27mer):

5' biotin-AACATGAATCTTTCGCTCGTCCTGGCT-3' (SEQ ID NO. 83)

based on the information of nucleotide sequence obtained by SST, plasmid hybridized specifically with the biotinylated primer were recovered from the cDNA library according to the method of Gene Trapper Kit and then transfected into E. Coli DH10B. Colony hybridization with ON056 SST cDNA which was labeled with ^{32}P-dCTP, as a probe, was performed by using Random Primer DNA Labeling kit (Trade name, marketed by Takara Shuzo Co.) according to known method to isolate the positive done and to prepare the plasmid. Nucleotide sequences of 5'-end were determined, and the existence of nucleotide sequence ON056 SST cDNA was confirmed. Nucleotide sequence of full-length ON056 SST cDNA was determined and then sequence shown in SEQ ID NO. 3 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 1 and 2, respectively, were obtained.

[0107] It was indicated from the results of homology search for the public database of the nucleic add sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of ON056 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0108] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone ON056 (region of 1st–334th amino add in SEQ ID NO. 1) and Human Cathepsin L (Swiss Prot Accession P07711) (region of 1st–334th amino acid) or between done ON056 (region of 22nd– 334th amino add in SEQ ID NO. 1) and Human Cathepsin K (Swiss Prot Accession P43235) (region of 19th–329th amino add). Based on these homologies, clone ON0566 and Human Cathepsin L family were expected to share at least some activity.

(5) Expression of protein using E. Coli

[0109] The coding region cDNA fragments without sequence encoding signal peptide were amplified by PCR and inserted into the downstream of initiation codon ATG in pET expression vector (marketed by Novagen Co.) for E. Coli inframe to construct the plasmid for expression. The obtained plasmids were transfected into E. Coli BL21 (DE3) and the transformant was cultured with IPTG to induce the expression of protein. The obtained E. Coli was harvested and lysed with ultra-sonication or detergent The insoluble fraction was solubilized with urea and subjected to SDS-PAGE. The expression of ON056 protein was confirmed by Coomassie staining (arrow in Fig. 1).

(6) Expression of the protein using mammalian cell

[0110] Thus obtained full-length cDNA was conjugated into XhoI (or EcoRI)-NotI site of the pED6 expression vector of mammalian cells (See Kaufman et al., Nucleic Adds Res. 19, 4485-4490 (1991)) to construct plasmid to express the secretory protein or membrane protein. The obtained plasmids were transfected into Cos 7 cells using Lypofectine (Trade name, marketed by GIBCO BRL Co.). After 24 hours, the transfection mixture was removed. The cells were cultured in the Met and Cys-free medium with ^{35}S-labeled Met and ^{35}S-labeled Cys for 5 hours. The supernatants were harvested and 10-fold concentrated with Centricon-10 (Trade name, marketed by Amicon Co.). The samples were separated on SDS-PAGE gels. After drying the acrylamidogel, the expression of ^{35}S-labeled protein was detected using BAS2000 (marketed by Fuji Film Co.).

Example 2: Clone ON034

[0111] In Example relating to clone ON034 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0112] Total RNA was prepared from human placenta tissue by TRIzol reagent. Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0113] A full-length cDNA was cloned using GENETRAPPER cDNA Positive Selection System. First, dT-primed cDNA library was prepared from poly (A)+RNA in human placenta tissue using pSPORT1 plasmid, as a vector, by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning. Next, after preparing biotinylated primer ON034-F1 (28mer):

5' biotin-TGAAGCCCATCACTACATCGCCATTACG-3' (SEQ ID NO.: 84)

based on the information of nucleotide sequence obtained by SST, plasmid hybridized specifically with the biotinylated primer were recovered from the cDNA library according to the method of Gene Trapper Kit and then transfected into E. Coli DH10B. Colony hybridization with ON034 SST cDNA which was labeled with 32P-dCTP, as a probe, was performed by using Random Primer DNA Labeling kit according to known method to isolate the positive done and to prepare the plasmid. Nucleotide sequence of full-length ON034 SST cDNA was determined by the same procedure as ON056 and then sequence shown in SEQ ID NO. 6 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 4 and 5, respectively, were obtained.

[0114] It was indicated from the results of homology search for the public database of the nucleic add sequences by using BLASTN and FASTA, and for the public database of the amino add sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of ON034 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 3: Clone OX003

[0115] In Example relating to clone OX003 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0116] Total RNA was prepared from human placenta tissue by TRIzol reagent. Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0117] A full-length cDNA was cloned using Marathon cDNA Amplification Kit (Trade name, marketed by Clontech Co.) according to 3' RACE (Rapid Amplification of cDNA End) method. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA in human placenta tissue. 27mer primer OX003-F1:

5'-CAAAACCCACAAGAAATTCACCAAGGC-3' (SEQ ID NOS. 85)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 23mer primer OX003-F2:

5'-TCACCAAGGCTAACATGGTGGCC-3' (SEQ ID NOS. 86)

was prepared additionally at 3' end of OX003-F1 primer and then nested PCR was performed. cDNA which was amplified with done OX003 specifically was separated with agarose-gel electrophoresis, ligated to pT7 Blue-2 T-Vector (Trade name, marketed by Novagen Co.) and transfected into E. Coli DH5a to prepare the plasmid. First, Nucleotide sequences of 5'-end were determined, and the existence of nucleotide sequence OX003 SST cDNA was confirmed. Nucleotide sequence of full-length OX003 SST cDNA was determined and then sequence shown in SEQ ID NO. 9 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 7 and 8, respectively, were obtained.

[0118] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino add sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OX003 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 4: Clone OA052

[0119] In Example relating to done OA052 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0120] Total RNA was prepared from human glioblastoma cell line T98G (ATCC No. CRL-1690) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0121] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA conjugating adapter was prepared from the origin of each clone, i.e., poly (A)$^+$RNA in human glioblastoma cell line T98G according to the method of the said kit 27mer primer OA052-F1:

5'-ATGCCTAGAAGAGGACTGATTCTTCAC-3' (SEQ ID NO. 87)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. cDNA which was amplified with done OA052 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 12 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 10 and 11, respectively, were obtained.

[0122] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino add sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OA052 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 5: Clone OC004

[0123] In Example relating to clone OC004 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0124] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0125] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each done, i.e., poly (A)$^+$RNA in human adult brain tissue. 27mer primer OC004-F1:

5'-ATGAGGAAAGGGAACCTTCTGCTGAGC-3' (SEQ ID NOS. 88)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 18mer primer OC004-F2:

5'-TGAGCTTCCAGAGCTGTC-3' (SEQ ID NOS. 89)

was prepared additionally at 3' end of OC004-F1 primer and then nested PCR was performed. cDNA which was amplified with done OC004 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 15 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 13 and 14, respectively, were obtained.

[0126] It was indicated from the results of homology search for the public database of the nucleic add sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OC004 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 6: Clone OM017

[0127] In Example relating to clone OM017 of the present invention, the same procedure as in Example of ON056

was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0128] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0129] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each done, i.e., poly (A)$^+$RNA in human adult brain tissue. 27mer primer OM017-F3:

5'-GGGAAATGAAACATTTCTGTAACCTGC-3' (SEQ ID NOS. 90)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 27mer primer OM017-F1:

5'-ATGAAACATTTCTGTAACCTGCTTTGT-3' (SEQ ID NOS. 91)

was prepared additionally at 3' end of OM017-F3 primer and then nested PCR was performed. cDNA which was amplified with clone OM017 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 18 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 16 and 17, respectively, were obtained.

[0130] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OM017 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0131] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OM017 (region of 433th~709th, 42nd~ 225th, 170th~399th and 1st~224th amino add in SEQ ID NO. 16) and Human DXS6673E (Candidate gene for Mental Retardation) (PRF Code 2218282A (Genbarik Accession X95808)) (region of 1083rd~1358th, 758th~ 932nd, 850th~1081st and 739th~965th amino add) Based on these homologies, clone OM017 and Human DXS6673E were expected to share at least some activity.

Example 7: Clone OM101

[0132] In Example relating to done OM101 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0133] Total RNA was prepared from human adult brain tissue by TRIzol reagent. Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0134] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA in human adult brain tissue. 27mer primer OM101-F3:

5'-TGAAGTTGCAGATAATGAGGACTTACC-3' (SEQ ID NOS. 92)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 27mer primer OM101-F1:

5'-ATGAGGACTTACCATTATATACCATTA-3' (SEQ ID NOS. 93)

was prepared additionally at 3' end of OM0101-F3 primer and then nested PCR was performed. cDNA which was amplified with done OM101 specifically was separated with redoning by the same method as Example of OX003. Full nucleotide sequence, was determined and then sequence shown in SEQ ID NO. 21 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 19 and 20, respectively, were obtained.

[0135] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OM101 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0136] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between done OM101 (region of 1st~77th amino acid in SEQ ID NO. 19), and a lot of Cadherin family such as Human Cadherin-6 (Swiss Prot Accession P55285) (region of 1st~77th amino acid) and Human Brain-Cadherin (Swiss Prot Accession P55289) (region of 1st~78th amino acid). Based on these homologies, done OM101 and Human Cadherin-6 and the other Cadherin family were expected to share at least some activity.

Example 8: Clone OM126

[0137] In Example relating to clone OM126 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0138] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0139] Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA in human adult brain tissue. 27mer primer OM126-F3:

5'-AGGAAGGATGAGGAAGACCAGGCTCTG-3' (SEQ ID NOS. 94)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with done OM126 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 24 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 22 and 23, respectively, were obtained.

[0140] It was indicated from the results of homology search for the public database of the nucleic add sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OM126 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0141] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OM126 (region of 25th~115th amino acid in SEQ ID NO. 22), and immunoglobulin domain. Based on these homologies, clone OM126 and immunoglobulin superfamily were expected to share at least some activity.

Example 9: Clone OM160

[0142] In Example relating to clone OM160 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0143] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0144] A full-length cDNA was cloned using GENETRAPPER cDNA Positive Selection System. First, dT-primed cDNA library was prepared from poly (A)+RNA in human adult brain tissue using pSPORT1 plasmid, as a vector, by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning. Next, after preparing biotinylated primer ON160-F1 (27mer):

5' biotin-ATGCTTCAGTGGAGGAGAAGACACTGC-3' (SEQ ID NO. 95)

based on the information of nucleotide sequence obtained by SST, plasmid hybridized specifically with the biotinylated

primer were recovered from the cDNA library according to the method of Gene Trapper Kit and then transfected into E. Coli DH10B. Colony hybridization with OM160 SST cDNA which was labeled with 32P-dCTP, as a probe, was performed by using Random Primer DNA Labeling kit according to known method to isolate the positive clone and to prepare the plasmid. Nucleotide sequence of full-length OM160 SST cDNA was determined by the same procedure as ON056 and then sequence shown in SEQ ID NO. 27 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 25 and 26, respectively, were obtained.

[0145] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OM160 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0146] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OM160 (region of 153rd~395th amino acid in SEQ ID NO. 25) and Drosophila neurogenic secreted signaling protein (Genepept Accession U41449) (region of 80th~317th amino acid). Based on these homologies, done OM160 and Drosophila neurogenic secreted signaling protein were expected to share at least some activity.

Example 10: Clone OMA016

[0147] In Example relating to clone OMA016 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0148] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0149] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA in human adult brain tissue. 27mer primer OMA016-F1:

5'-AGAAATGGTGAATGCCTGCTGGTGTGG-3' (SEQ ID NOS. 96)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. There existed two kinds of cDNAs which were amplified with clone OMA016 specifically and which were named OMA016a and OMA016b. These two were separated with recloning by the same method as Example of OX003. Full nucleotide sequences were determined and then sequences shown in SEQ ID NOS. 30 and 33 were obtained. Each open reading frame was determined and reduced amino acid sequences and nucleotide sequences shown in SEQ ID NOS. 28, 31 and SEQ ID NOS. 29, 32, respectively, were obtained.

[0150] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OMA016a and OMA016b of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 11: Clone OMB130

[0151] In Example relating to clone OMB130 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0152] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0153] Double strand cDNA was prepared from the origin of each clone, i.e., poly $(A)^+$RNA in human adult brain tissue. 27mer primer OMB130-F1:

5'-TCCTCTGACTTTTCTTCTGCAAGCTCC-3' (SEQ ID NOS. 97)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with done OMB130 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 36 was obtained. An open reading frame was determined and deduced amino add sequence and nucleotide sequence shown in SEQ ID NOS. 34 and 35, respectively, were obtained.

[0154] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OMB130 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0155] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OMB130 (region of 10th~177th amino acid in SEQ ID NO. 34), and Monkey Hepatitis A virus receptor (PRF Code 2220266A (Genbank Accession X98252) (region of 6th~173rd amino acid. Based on these homologies, clone OMB130 and Monkey Hepatitis A virus receptor were expected to share at least some activity.

Example 12: Clone OMB142

[0156] In Example relating to clone OMB142 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly$(A)^+$RNA

[0157] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly$(A)^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0158] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each done, i.e., poly $(A)^+$RNA in human adult brain tissue. 27mer primer OMB142-F2:

5'-GCCCAAGGTCAAGGAGATGGTACGGAT-3' (SEQ ID NOS. 98)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 28mer primer OMB142-F1:

5'-GGAGATGGTACGGATCTTAAGGACTGTG-3' (SEQ ID NOS. 99)

was prepared additionally at 3' end of OMB142-F2 primer and then nested PCR was performed. cDNA which was amplified with done OMB142 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 39 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 37 and 38, respectively, were obtained.

[0159] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OMB142 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 13: Clone OTB033

[0160] In Example relating to clone OTB033 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0161] Total RNA was prepared from human neuroblastoma cell line IMR-32 (ATCC No. CCL-127) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0162] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of IMR-32. 27mer primer OTB033-F1:

5'-TGCACTATCCAAAAGCTCCATGTACAC-3' (SEQ ID NOS. 100)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 19mer primer OTB003-F2:

5'-CCATGTACACAGTGGGGGC-3' (SEQ ID NOS. 101)

was prepared additionally at 3' end of OTB033-F1 primer and then nested PCR was performed. cDNA which was amplified with clone OTB033 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 42 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 40 and 41, respectively, were obtained.

[0163] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OTB033 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 14: Clone OVB100

[0164] In Example relating to clone OVB100 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0165] Total RNA was prepared from human astrocytoma cell line CCF-STTG1 (ATCC No. CRL-1718) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0166] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of CCF-STTG1. 27mer primer OVB100-F1:

5'-CACTTGGTGTTTGATTTACCTAAGCAC-3' (SEQ ID NOS. 102)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with done OVB100 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 45 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 43 and 44, respectively, were obtained.

[0167] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OVB100 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 15: Clone OAF062

[0168] In Example relating to clone OAF062 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0169] Total RNA was prepared from human bone marrow stroma cell line HAS303 (provided from Prof. Keisuke Sotoyama, Dr. Makoto Aizawa, First Medicine, Tokyo Medical College) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0170] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of HAS303. 27mer primer OAF062-F2:

5'-GAGTTTCGTAAGCAAAATAGAGGACAG-3' (SEQ ID NOS. 103)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 27mer primer OAF062-F3:

5'-TAGAGGACAGAAATGCAGTTCATGAAC-3' (SEQ ID NOS. 104)

was prepared additionally at 3' end of OAF062-F2 primer and then nested PCR was performed. cDNA which was amplified with clone OAF062 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 48 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 46 and 47, respectively, were obtained.

[0171] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAF062 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 16: Clone OAF075

[0172] In Example relating to clone OAF075 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0173] Total RNA was prepared from human bone marrow stroma cell line HAS303 (provided from Prof. Keisuke Sotoyama, Dr. Makoto Aizawa, First Medicine, Tokyo Medical College) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0174] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of HAS303. 28mer primer OAF075-F1:

5'-GACATGAGGTGGATACTGTTCATTGGGG-3' (SEQ ID NOS. 105)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with clone OAF075 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 51 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 49 and 50, respectively, were obtained.

[0175] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAF075 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0176] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OAF075 (region of 1st–421st amino acid in SEQ ID NO. 49), and Human Carboxypeptidase A2 (Swiss Prot Accession P48052) (region of 1st–417th amino acid), Human Carboxypeptidase A1 (Swiss Prot Accession P15085) (region of

1st~417th amino acid), Human Carboxypeptidase B (Swiss Prot Accession P15086) (region of 5th~416th amino acid) and Human Mast Cell Carboxypeptidase A (Swiss Prot Accession P15088) (region of 1st~412th amino acid) . Based on these homologies, clone OAF075 and Carboxypeptidase family were expected to share at least some activity.

Example 17: Clone OAG119

[0177] In Example relating to clone OAG119 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0178] Total RNA was prepared from human bone marrow stroma cell line LP101 (provided from Prof. Keisuke Sotoyama, Dr. Makoto Aizawa, First Medicine, Tokyo Medical College) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0179] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of LP101. 28mer primer OAG119-F1:

5'-TGGCGTGTAACTATGCTCATCATTGTTC-3' (SEQ ID NOS. 106)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with done OAG119 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 54 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 52 and 53, respectively, were obtained.

[0180] It was indicated from the results of homology search for the public database of the nucleic add sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAG119 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 18: Clone OAH040

[0181] In Example relating to clone OAH040 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0182] Total RNA was prepared from endothelial cell line of vein derived from human umbilical cord UV-EC-C (ATCC No. CRL-1730) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0183] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of HUV-EC-C. 28mer primer OAH040-F1:

5'-TTAGCCCACCCATGTTGATAGAACACCC-3' (SEQ ID NOS. 107)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with clone OAH040 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 57 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 55 and 56, respectively, were obtained.

[0184] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAH040 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 19: Clone OAH058

[0185] In Example relating to clone OAH058 of the present invention, the same procedure as in Example of OAH056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0186] Total RNA was prepared from endothelial cell line of vein derived from human umbilical cord HUV-EC-C (ATCC No. CRL-1730) by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0187] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of HUV-EC-C. 28mer primer OAH058-F1:

5'-ACAATGTTGGCCTGTC TGCAAGCTTGTG-3' (SEQ ID NOS. 108)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with done OAH058 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 60 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 58 and 59, respectively, were obtained.

[0188] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAH058 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

Example 20: Clone OM011

[0189] In Example relating to clone OM011 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0190] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0191] A full-length cDNA was cloned using GENETRAPPER cDNA Positive Selection System. First, dT-primed cDNA library was prepared from poly (A)+RNA in human adult brain tissue using pSPORT1 plasmid, as a vector, by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning. Next, after preparing biotinylated primer OM011-F1 (27mer):

5' biotin-GAAGTGACTCTTCCTCTAGTTTGCCAC-3' (SEQ ID NOS. 109)

based on the information of nucleotide sequence obtained by SST, plasmid hybridized specifically with the biotinylated primer were recovered from the cDNA library according to the method of Gene Trapper Kit and then transfected into E. Coli DH10B. Colony hybridization with OM011 SST cDNA which was labeled with 32P-dCTP, as a probe, was performed by using Random Primer DNA Labeling kit according to known method to isolate the positive clone and to prepare the plasmid. Nucleotide sequence of full-length OM011 SST cDNA was determined by the same procedure as ON056 and then sequence shown in SEQ ID NO. 63 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 61 and 62, respectively, were obtained.

[0192] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OM011 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0193] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone

OM011 (region of 26th–396th amino acid in SEQ ID NO. 61) and Human Plasma-cell Glycoprotein PC-1 (Alkaline Phosphodiesterase I) (Swiss Prot Accession P22413) (region of 158th–543rd amino acid). Based on these homologies, done OM011 and Human Plasma-cell Glycoprotein PC-1 were expected to share at least some activity.

Example 21: Clone OM028

[0194] In Example relating to done OM028 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0195] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0196] A full-length cDNA was cloned using GENETRAPPER cDNA Positive Selection System. First, dT-primed cDNA library was prepared from poly (A)+RNA in human adult brain tissue using pSPORT1 plasmid, as a vector, by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning. Next, after preparing biotinylated primer OM028-F1 (27mer):

5' biotin-ATGAAGGACATGCCACTCCGAATTCAT-3' (SEQ ID NOS. 110)

based on the information of nucleotide sequence obtained by SST, plasmid hybridized specifically with the biotinylated primer were recovered from the cDNA library according to the method of Gene Trapper Kit and then transfected into E. Coli DH10B. Colony hybridization with OM028 SST cDNA which was labeled with 32P-dCTP, as a probe, was performed by using Random Primer DNA Labeling kit according to known method to isolate the positive done and to prepare the plasmid. Nucleotide sequence of full-length OM028 SST cDNA was determined by the same procedure as ON056 and then sequence shown in SEQ ID NO. 66 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 64 and 65, respectively, were obtained.

[0197] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OM028 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0198] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OM028 (region of 1st–708th amino acid in SEQ ID NO. 64) and many proteins containing Leu-rich repeat such as Mouse Leu-rich repeat protein (PRF Code 2212307A (GENBANK Accession D49802) (region of 1st–707th amino acid). Based on these homologies, clone OM028 and certain proteins containing Leu-rich repeat were expected to share at least some activity.

Example 22: Clone OMB092

[0199] In Example relating to clone OMB092 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0200] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0201] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA in human adult brain tissue. 27mer primer OMB092-F1:

5'-ACTCACCTGGATCCCTAAGGGCACAGC-3' (SEQ ID NOS. 111)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient ampli-

fication of cDNA by only one-time PCR, 28mer primer OMB092-F2:

5'-AGAATGAGCTATTACGGCAGCAGCTATC-3' (SEQ ID NOS. 112)

was prepared additionally at 3' end of OMB092-F1 primer and then nested PCR was performed. cDNA which was amplified with clone OMB092 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 69 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 67 and 68, respectively, were obtained.

[0202] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OMB092 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0203] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OMB092 (region of 1st~254th amino acid in SEQ ID NO. 67) and many Potassium Channels family such as Rat Inward Rectifier Potassium Channel BIR9 (Swiss Prot Accession P52191) (region of 1st~254th amino acid). Based on these homologies, clone OMB092 and Potassium Channel were expected to share at least some activity.

Example 23: Clone OMB108

[0204] In Example relating to clone OMB108 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0205] Total RNA was prepared from human adult brain tissue by TRIzol reagent Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0206] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA in human adult brain tissue. 27mer primer OMB108-F1:

5'-CTCTCTCCATCTGCTGTGGTTATGGCC-3' (SEQ ID NOS. 113)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. PCR was performed with the said primer and adapter primer attached in the kit. Due to insufficient amplification of cDNA by only one-time PCR, 22mer primer OMB108-F2:

5'-TGGTTATGGCCTGTCGCTGGAG-3' (SEQ ID NOS. 114)

was prepared additionally at 3' end of OMB108-F1 primer and then nested PCR was performed. cDNA which was amplified with done OMB108 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 72 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 70 and 71, respectively, were obtained.

[0207] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OMB108 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0208] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OMB108 (region of 164th~256th and 374th~487th amino add in SEQ ID NO. 70) and LDL-repeat region of many LDL receptors family such as Human Low-Density Lipoprotein Receptor Related Protein 10 (Swiss Prot Accession Q07954) or OMB108 (region of 47th ~158th and 259th~370th amino add in SEQ ID NO. 70) and CUB domain included in Human Bone Morphogenetic Protein 1 (Swiss Prot Accession P13497). That is to say, clone OMB108 proved to possess the common sequences of two parts of CUB domain and five parts of LDL-repeat at the extracell domain. Based on these homologies, clone OMB108, protein including LDL-repeat and protein including CUB domain were expected to share at least some activity.

Example 24: Clone OT007

[0209] In Example relating to clone OT007 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0210] Total RNA was prepared from human neuroblastoma cell line IMR-32 (ATCC No. CCL-127) by TRIzol reagent. Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0211] A full-length cDNA was cloned using GENETRAPPER cDNA Positive Selection System. First, dT-primed cDNA library was prepared from poly (A)+RNA in IMR-32 using pSPORT1 plasmid, as a vector, by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning. Next, after preparing biotinylated primer OT007-F1 (27mer):

5' biotin-AAAATGACTCCCCAGTCGCTGCTGCAG-3' (SEQ ID NOS. 115)

based on the information of nucleotide sequence obtained by SST, plasmid hybridized specifically with the biotinylated primer were recovered from the cDNA library according to the method of Gene Trapper Kit and then transfected into E. Coli DH10B. Colony hybridization with OT007 SST cDNA which was labeled with 32P-dCTP, as a probe, was performed by using Random Primer DNA Labeling kit according to known method to isolate the positive clone and to prepare the plasmid. Nucleotide sequence of full-length OT007 SST cDNA was determined by the same procedure as ON056 and then sequence shown in SEQ ID NO. 75 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 73 and 74, respectively, were obtained.

[0212] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OT007 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0213] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OT007 (region of 217th~660th amino acid in SEQ ID NO. 73) and transmembrane region of Secretin/Vasoactive Intestinal Peptide receptor superfamily such as Human Seven Transmembrane-domain receptor (Genepept Accession X82892), Rat Latrophilin-related protein 1 (Genepept Accession U78105), Human CD97 (Swiss Prot Accession P48960) etc. Based on these homologies, clone OT007 and certain proteins containing seven transmembrane region type of Secretin/Vasoactive Intestinal Peptide were expected to share at least some activity.

Example 25: Clone OAG051

[0214] In Example relating to clone OAG051 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0215] Total RNA was prepared from human bone marrow stroma cell line LP101 (provided from Prof. Keisuke Sotoyama, Dr. Makoto Aizawa, First Medicine, Tokyo Medical College) by TRIzol reagent. Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0216] A full-length cDNA was cloned using Marathon cDNA Amplification Kit according to 3' RACE method as described in Example of OX003. Double strand cDNA was prepared from the origin of each clone, i.e., poly (A)$^+$RNA of LP101. 27mer primer OAG051-F1:

5'-GGAAATGTTTACATTTTT GTTGACGTG-3' (SEQ ID NOS. 116)

containing the deduced initiation ATG codon region based on the information of nucleotide sequence obtained by SST, was prepared. cDNA which was amplified with clone OAG051 specifically was separated with recloning by the same method as Example of OX003. Full nucleotide sequence was determined and then sequence shown in SEQ ID NO. 78 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 76 and 77, respectively, were obtained.

[0217] It was indicated from the results of homology search for the public database of the nucleic acid sequences

by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OAG051 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0218] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OAG051 and many Frizzled family, for example, clone OAG051 (region of 4th~703rd amino acid in SEQ ID NO. 76) and Mouse Frizzled-6 (PRF Code2208383E (Genebank Accession U43319) (region of 6th~708th amino acid) or clone OAG051 (region of 1st~627th amino acid in SEQ ID NO. 76) and Mouse Frizzled-3 (PRF Code 2208383E (Genebank Accession U43205) (region of 7th~618th amino acid). Based on these homologies, clone clone OAG051 and Frizzled family were expected to share at least some activity.

Example 26: Clone OUB068

[0219] In Example relating to clone OUB068 of the present invention, the same procedure as in Example of ON056 was used except for the following points.

(1) Preparation of Poly(A)$^+$RNA

[0220] Total RNA was prepared from human osteosarcoma cell line U-2OS (ATCC No. HTB-96) by TRIzol reagent. Poly(A)$^+$RNA was purified from the total RNA by mRNA Purification Kit.

(2) Cloning of a full-length cDNA and determination of nucleotide sequence

[0221] A full-length cDNA was cloned using GENETRAPPER cDNA Positive Selection System. First, dT-primed cDNA library was prepared from poly (A)+RNA in U-2OS using pSPORT1 plasmid, as a vector, by Super Script Plasmid System for cDNA Synthesis and Plasmid Cloning. Next, after preparing biotinylated primer OUB068-F1 (27mer):

5' biotin-CACTCATGAAGGAAATTCCAGCGCTGC-3' (SEQ ID NOS. 117)

based on the information of nucleotide sequence obtained by SST, plasmid hybridized specifically with the biotinylated primer were recovered from the cDNA library according to the method of Gene Trapper Kit and then transfected into E. Coli DH10B. Colony hybridization with OUB068 SST cDNA which was labeled with 32P-dCTP, as a probe, was performed by using Random Primer DNA Labeling kit according to known method to isolate the positive clone and to prepare the plasmid. Nucleotide sequence of full-length OUB068 SST cDNA was determined by the same procedure as ON056 and then sequence shown in SEQ ID NO. 81 was obtained. An open reading frame was determined and deduced amino acid sequence and nucleotide sequence shown in SEQ ID NOS. 79 and 80, respectively, were obtained.

[0222] It was indicated from the results of homology search for the public database of the nucleic acid sequences by using BLASTN and FASTA, and for the public database of the amino acid sequences by using BLASTX, BLASTP and FASTA, that there was no sequence identical to the polypeptide sequence and the nucleotide sequence of OUB068 of the present invention. From these results, it was proved that polypeptide of the present invention was new secretary protein.

[0223] However, the search using BLASTX, BLASTP and FASTA revealed a significant homology between clone OUB068 (region of 5th~386th amino acid in SEQ ID NO. 79) and Xenopus Unknown Transmembrane Protein (Genepept Accession X92871) (region of 3rd~407th amino acid). Based on these homologies, clone OUB068 and Xenopus Unknown Transmembrane Protein were expected to share at least some activity.

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atttcagcag ccttcgggtt gttacatatt tattcttttt tgaagcccat cactacatcg  120
ccattacgtt ttacactgtg tatgtaacaa atg tta cca ctt tgt tct tta ttc    174
                                Met Leu Pro Leu Cys Ser Leu Phe
                                -14             -10
ctt ttt gga tca tct tca gtg ggg gta aaa cag tat caa gct cta gag     222
Leu Phe Gly Ser Ser Ser Val Gly Val Lys Gln Tyr Gln Ala Leu Glu
 -5                  1               5                  10
ctc cct ctg gtg gtt ttt gtg aca tat ttg aag atg gca gct tgc ttt     270
Leu Pro Leu Val Val Phe Val Thr Tyr Leu Lys Met Ala Ala Cys Phe
             15                  20                  25
ttg aga att tct ggc tct gct ctc cct gtt ttt atc tgt act ttt ttt     318
Leu Arg Ile Ser Gly Ser Ala Leu Pro Val Phe Ile Cys Thr Phe Phe
         30                  35                  40
tct cat tgt gcc tct tgc aca cac aca ccc ctt ccc cac cat cta ccc     366
Ser His Cys Ala Ser Cys Thr His Thr Pro Leu Pro His His Leu Pro
     45                  50                  55
aat ttg cgc ctg ttc cag cag ttt ctc ttc agg gca ggg ccg tgt tgg     414
Asn Leu Arg Leu Phe Gln Gln Phe Leu Phe Arg Ala Gly Pro Cys Trp
 60                  65                  70
gac atg att tct att aag agt gag ggc cca aat tgc tct tgc ccc tgc     462
Asp Met Ile Ser Ile Lys Ser Glu Gly Pro Asn Cys Ser Cys Pro Cys
 75                  80                  85                  90
agc cct tat cac aga ccc ctg tagtcattat tggaacatgc tgttcttggg        513
Ser Pro Tyr His Arg Pro Leu
                 95
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cctgctttic tcagtcactg gagttctcca gtttgtaaga cggctcctcg cctcccctct 573
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<211> 111
<212> PRT
<213> Homo sapiens

<400> 7

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Gly	Leu	Asn	Leu	Ala	Pro	Ala	Thr	Gly	Gly	Gly	Ser	Leu	Leu	Leu	Ser
-10				-5				1					5		
Thr	Ala	Gly	Gln	Gly	Leu	Ala	Thr	Ala	Ala	Gly	Val	Thr	Ser	Ile	Val
			10					15					20		
Ser	Gly	Thr	Leu	Glu	Arg	Ser	Lys	Asn	Lys	Glu	Ala	Gln	Ala	Arg	Ala
		25					30					35			
Glu	Asp	Ile	Leu	Pro	Thr	Tyr	Asp	Gln	Glu	Asp	Arg	Glu	Asp	Glu	Glu
	40					45					50				
Glu	Lys	Ala	Asp	Tyr	Val	Thr	Ala	Ala	Gly	Lys	Ile	Ile	Tyr	Asn	Leu
55					60					65					70
Arg	Asn	Thr	Leu	Lys	Tyr	Ala	Lys	Lys	Asn	Val	Arg	Ala	Phe	Trp	
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<213> Homo sapiens

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gcagctgggg tcaccagcat cgtgagtggt acgttggaac gctccaaaaa taaagaagcc 180
caagcacggg cggaagacat actgcccacc tacgaccaag aggacaggga ggatgaggaa 240
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aagtatgcca agaaaaacgt ccgtgcattt tgg 333

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tgccctcgca gacgatattg acaaaaccca caagaaattc accaaggcta ac atg 175
Met
-26
gtg gcc acc tct act gct gtc atc tct gga gtg atg agc ctc ctg ggt 223
Val Ala Thr Ser Thr Ala Val Ile Ser Gly Val Met Ser Leu Leu Gly
-25 -20 -15 -10
tta gcc ctt gcc cca gca acg gga gga gga agc ctg ctg ctc tcc acc 271

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Leu Ala Leu Ala Pro Ala Thr Gly Gly Gly Ser Leu Leu Leu Ser Thr
                -5                  1               5

gct ggt caa ggt ttg gca aca gca gct ggg gtc acc agc atc gtg agt    319
Ala Gly Gln Gly Leu Ala Thr Ala Ala Gly Val Thr Ser Ile Val Ser
        10                  15                  20

ggt acg ttg gaa cgc tcc aaa aat aaa gaa gcc caa gca cgg gcg gaa    367
Gly Thr Leu Glu Arg Ser Lys Asn Lys Glu Ala Gln Ala Arg Ala Glu
    25                  30                  35

gac ata ctg ccc acc tac gac caa gag gac agg gag gat gag gaa gag    415
Asp Ile Leu Pro Thr Tyr Asp Gln Glu Asp Arg Glu Asp Glu Glu Glu
40                  45                  50                  55

aag gca gac tat gtc aca gct gct gga aag att atc tat aat ctt aga    463
Lys Ala Asp Tyr Val Thr Ala Ala Gly Lys Ile Ile Tyr Asn Leu Arg
                60                  65                  70

aac acc ttg aag tat gcc aag aaa aac gtc cgt gca ttt tgg            505
Asn Thr Leu Lys Tyr Ala Lys Lys Asn Val Arg Ala Phe Trp
            75                  80                  85

taactcagag ccaacccacg ctcggccaat gctaccaagc gtcttctgac cactggccaa  565
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<210> 10
<211> 542
<212> PRT
<213> Homo sapiens

<400> 10

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Leu	Gly	Leu	Ala	Leu	Leu	Cys	Ser	Leu	Val	Leu	Phe	Met	Tyr	Leu	Leu
		-15					-10					-5			
Glu	Cys	Ala	Pro	Gln	Thr	Asp	Gly	Asn	Ala	Ser	Leu	Pro	Gly	Val	Val
	1				5					10					
Gly	Glu	Asn	Tyr	Gly	Lys	Glu	Tyr	Tyr	Gln	Ala	Leu	Leu	Gln	Glu	Gln
15				20				25					30		
Glu	Glu	His	Tyr	Gln	Thr	Arg	Ala	Thr	Ser	Leu	Lys	Arg	Gln	Ile	Ala
			35				40					45			
Gln	Leu	Lys	Gln	Glu	Leu	Gln	Glu	Met	Ser	Glu	Lys	Met	Arg	Ser	Leu
		50					55					60			
Gln	Glu	Arg	Arg	Asn	Val	Gly	Ala	Asn	Gly	Ile	Gly	Tyr	Gln	Ser	Asn

65 70 75

Lys Glu Gln Ala Pro Ser Asp Leu Leu Glu Phe Leu His Ser Gln Ile

80 85 90

Asp Lys Ala Glu Val Ser Ile Gly Ala Lys Leu Pro Ser Glu Tyr Gly

95 100 105 110

Val Ile Pro Phe Glu Ser Phe Thr Leu Met Lys Val Phe Gln Leu Glu

115 120 125

Met Gly Leu Thr Arg His Pro Glu Glu Lys Pro Val Arg Lys Asp Lys

130 135 140

Arg Asp Glu Leu Val Glu Val Ile Glu Ala Gly Leu Glu Val Ile Asn

145 150 155

Asn Pro Asp Glu Asp Asp Glu Gln Glu Asp Glu Glu Gly Pro Leu Gly

160 165 170

Glu Lys Leu Ile Phe Asn Glu Asn Asp Phe Val Glu Gly Tyr Tyr Arg

175 180 185 190

Thr Glu Arg Asp Lys Gly Thr Gln Tyr Glu Leu Phe Phe Lys Lys Ala

195 200 205

Asp Leu Thr Glu Tyr Arg His Val Thr Leu Phe Arg Pro Phe Gly Pro

210 215 220

Leu Met Lys Val Lys Ser Glu Met Ile Asp Ile Thr Arg Ser Ile Ile

225 230 235

Asn Ile Ile Val Pro Leu Ala Glu Arg Thr Glu Ala Phe Val Gln Phe

240 245 250

Met Gln Asn Phe Arg Asp Val Cys Ile His Gln Asp Lys Lys Ile His

255 260 265 270

Leu Thr Val Val Tyr Phe Gly Lys Glu Gly Leu Ser Lys Val Lys Ser

275 280 285

Ile Leu Glu Ser Val Thr Ser Glu Ser Asn Phe His Asn Tyr Thr Leu

290 295 300

Val Ser Leu Asn Glu Glu Phe Asn Arg Gly Arg Gly Leu Asn Val Gly

305 310 315

Ala Arg Ala Trp Asp Lys Gly Glu Val Leu Met Phe Phe Cys Asp Val

320 325 330

Asp Ile Tyr Phe Ser Ala Glu Phe Leu Asn Ser Cys Arg Leu Asn Ala

335 340 345 350

Glu Pro Gly Lys Lys Val Phe Tyr Pro Val Val Phe Ser Leu Tyr Asn

355 360 365

Pro Ala Ile Val Tyr Ala Asn Gln Glu Val Pro Pro Pro Val Glu Gln

370 375 380

Gln Leu Val His Lys Lys Asp Ser Gly Phe Trp Arg Asp Phe Gly Phe

385 390 395

Gly Met Thr Cys Gln Tyr Arg Ser Asp Phe Leu Thr Ile Gly Gly Phe

400 405 410

Asp Met Glu Val Arg Gly Trp Gly Gly Glu Asp Val His Leu Tyr Arg

415 420 425 430

Lys Tyr Leu His Gly Asp Leu Ile Val Ile Arg Thr Pro Val Pro Gly

435 440 445

Pro Phe His Leu Trp His Glu Lys Arg Cys Ala Asp Glu Leu Thr Pro

450 455 460

Glu Gln Tyr Arg Met Cys Ile Gln Ser Lys Ala Met Asn Glu Ala Ser

465 470 475

His Ser His Leu Gly Met Leu Val Phe Arg Glu Glu Ile Glu Thr His

480 485 490

Leu His Lys Gln Ala Tyr Arg Thr Asn Ser Glu Ala Val Gly

495 500 505

<210> 11

<211> 1626

<212> DNA

<213> Homo sapiens

<400> 11

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ctacaggaac aagaagaaca ttatcagacc agggcaacca gtctgaaacg ccaaattgcc 240

caactaaaac aagaattaca agaaatgagt gaggagatgc ggtcactgca agaaagaagg 300

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                                          -34             -30

ctg att ctt cac acc cgg acc cac tgg ttg ctg ttg ggc ctt gct ttg     103
Leu Ile Leu His Thr Arg Thr His Trp Leu Leu Leu Gly Leu Ala Leu
            -25                 -20                 -15

ctc tgc agt ttg gta tta ttt atg tac ctc ctg gaa tgt gcc ccc cag     151
Leu Cys Ser Leu Val Leu Phe Met Tyr Leu Leu Glu Cys Ala Pro Gln
        -10                 -5                  1

act gat gga aat gca tct ctt cct ggt gtt gtt ggg gaa aat tat ggt     199
Thr Asp Gly Asn Ala Ser Leu Pro Gly Val Val Gly Glu Asn Tyr Gly
    5                   10                  15

aaa gag tat tat caa gcc ctc cta cag gaa caa gaa gaa cat tat cag     247
Lys Glu Tyr Tyr Gln Ala Leu Leu Gln Glu Gln Glu Glu His Tyr Gln
20                  25                  30                  35

acc agg gca acc agt ctg aaa cgc caa att gcc caa cta aaa caa gaa     295
Thr Arg Ala Thr Ser Leu Lys Arg Gln Ile Ala Gln Leu Lys Gln Glu
                40                  45                  50

tta caa gaa atg agt gag aag atg cgg tca ctg caa gaa aga agg aat     343
Leu Gln Glu Met Ser Glu Lys Met Arg Ser Leu Gln Glu Arg Arg Asn
            55                  60                  65

gta ggg gct aat ggc ata ggc tat cag agc aac aaa gag caa gca cct     391
Val Gly Ala Asn Gly Ile Gly Tyr Gln Ser Asn Lys Glu Gln Ala Pro
        70                  75                  80

agt gat ctt tta gag ttt ctt cat tcc caa att gac aaa gct gaa gtt     439
Ser Asp Leu Leu Glu Phe Leu His Ser Gln Ile Asp Lys Ala Glu Val
    85                  90                  95

agc ata ggg gcc aaa cta ccc agt gag tat ggg gtc att ccc ttt gaa     487
Ser Ile Gly Ala Lys Leu Pro Ser Glu Tyr Gly Val Ile Pro Phe Glu
100                 105                 110                 115

agt ttt acc tta atg aaa gta ttt caa ttg gaa atg ggt ctc act cgc     535
Ser Phe Thr Leu Met Lys Val Phe Gln Leu Glu Met Gly Leu Thr Arg
                120                 125                 130

cat cct gaa gaa aag cca gtt aga aaa gac aaa cga gat gaa ttg gtg     583
His Pro Glu Glu Lys Pro Val Arg Lys Asp Lys Arg Asp Glu Leu Val
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                135                 140                 145
gaa gtt att gaa gcg ggc ttg gag gtc att aat aat cct gat gaa gat    631
Glu Val Ile Glu Ala Gly Leu Glu Val Ile Asn Asn Pro Asp Glu Asp
        150                 155                 160
gat gaa caa gaa gat gag gag ggt ccc ctt gga gag aaa ctg ata ttt    679
Asp Glu Gln Glu Asp Glu Glu Gly Pro Leu Gly Glu Lys Leu Ile Phe
    165                 170                 175
aat gaa aat gac ttc gta gaa ggt tat tat cgc act gag aga gat aag    727
Asn Glu Asn Asp Phe Val Glu Gly Tyr Tyr Arg Thr Glu Arg Asp Lys
180                 185                 190                 195
ggc aca cag tat gaa ctc ttt ttt aag aaa gca gac ctt acg gaa tat    775
Gly Thr Gln Tyr Glu Leu Phe Phe Lys Lys Ala Asp Leu Thr Glu Tyr
                200                 205                 210
aga cat gtg acc ctc ttc cgc cct ttt gga cct ctc atg aaa gtg aag    823
Arg His Val Thr Leu Phe Arg Pro Phe Gly Pro Leu Met Lys Val Lys
            215                 220                 225
agt gag atg att gac atc act aga tca att att aat atc att gtg cca    871
Ser Glu Met Ile Asp Ile Thr Arg Ser Ile Ile Asn Ile Ile Val Pro
        230                 235                 240
ctt gct gaa aga act gaa gca ttt gta caa ttt atg cag aac ttc agg    919
Leu Ala Glu Arg Thr Glu Ala Phe Val Gln Phe Met Gln Asn Phe Arg
    245                 250                 255
gat gtt tgt att cat caa gac aag aag att cat ctc aca gtg gtg tat    967
Asp Val Cys Ile His Gln Asp Lys Lys Ile His Leu Thr Val Val Tyr
260                 265                 270                 275
ttt ggt aaa gaa gga ctg tct aag gtc aag tct atc cta gaa tct gtc   1015
Phe Gly Lys Glu Gly Leu Ser Lys Val Lys Ser Ile Leu Glu Ser Val
                280                 285                 290
acc agt gag tct aat ttt cac aat tac acc ttg gtc tca ttg aat gaa   1063
Thr Ser Glu Ser Asn Phe His Asn Tyr Thr Leu Val Ser Leu Asn Glu
            295                 300                 305
gaa ttt aat cgt gga cga gga cta aat gtg ggt gcc cga gct tgg gac   1111
Glu Phe Asn Arg Gly Arg Gly Leu Asn Val Gly Ala Arg Ala Trp Asp
        310                 315                 320
aag gga gag gtc ttg atg ttt ttc tgt gat gtt gat atc tat ttc tca   1159
Lys Gly Glu Val Leu Met Phe Phe Cys Asp Val Asp Ile Tyr Phe Ser
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    325                 330                 335
gcc gaa ttc ctt aac agc tgc cgg tta aat gct gag cca ggt aag aag   1207
Ala Glu Phe Leu Asn Ser Cys Arg Leu Asn Ala Glu Pro Gly Lys Lys
340                 345                 350                 355
gtg ttt tac cct gtg gtg ttc agt ctt tac aat cct gcc att gtt tat   1255
Val Phe Tyr Pro Val Val Phe Ser Leu Tyr Asn Pro Ala Ile Val Tyr
                360                 365                 370
gcc aac cag gaa gtg cca cca cct gtg gag cag cag ctg gtt cac aaa   1303
Ala Asn Gln Glu Val Pro Pro Pro Val Glu Gln Gln Leu Val His Lys
            375                 380                 385
aag gat tct ggc ttt tgg cga gat ttt ggc ttt gga atg act tgt cag   1351
Lys Asp Ser Gly Phe Trp Arg Asp Phe Gly Phe Gly Met Thr Cys Gln
        390                 395                 400
tat cgt tca gat ttc ctg acc att ggt gga ttt gac atg gaa gtg aga   1399
Tyr Arg Ser Asp Phe Leu Thr Ile Gly Gly Phe Asp Met Glu Val Arg
    405                 410                 415
ggt tgg ggt gga gaa gat gtt cat ctt tat cga aaa tac tta cat ggt   1447
Gly Trp Gly Gly Glu Asp Val His Leu Tyr Arg Lys Tyr Leu His Gly
420                 425                 430                 435
gac ctc att gtg att cgg act ccg gtt cct ggt cct ttc cac ctc tgg   1495
Asp Leu Ile Val Ile Arg Thr Pro Val Pro Gly Pro Phe His Leu Trp
                440                 445                 450
cat gaa aag cgc tgt gct gat gag ctg acc ccc gag cag tac cgc atg   1543
His Glu Lys Arg Cys Ala Asp Glu Leu Thr Pro Glu Gln Tyr Arg Met
            455                 460                 465
tgc atc cag tct aaa gcc atg aat gag gcc tct cac tcc cac ctg gga   1591
Cys Ile Gln Ser Lys Ala Met Asn Glu Ala Ser His Ser His Leu Gly
        470                 475                 480
atg ctg gtc ttc agg gag gaa ata gag acg cat ctt cat aaa cag gca   1639
Met Leu Val Phe Arg Glu Glu Ile Glu Thr His Leu His Lys Gln Ala
    485                 490                 495
tac agg aca aac agt gaa gct gtt ggt tgaaatcata attaatgcgt         1686
Tyr Arg Thr Asn Ser Glu Ala Val Gly
500                 505
tactgtatga accacaaaac agcactattt atttagcctt actctactt ccagatgcag  1746
tgcctctttt ggagaagaca tgttttattt tcatgttctt tctgacatta ctttagcaat  1806
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<213> Homo sapiens

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-17 -15 -10 -5

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1 5 10 15

Leu Lys Phe Ser Cys Trp Trp Glu Pro Arg Lys Thr Ala Gly Val Leu
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Thr Trp Pro Phe Leu Ala Glu Leu Ala Glu Val Gly Val Leu Ala Asp
35 40 45

Gly Met Tyr Leu Gly Ala Val Ser Val Ala Gln Gln Arg Cys Arg Ala
50 55 60

Asp Trp Leu Ser His Trp Val Leu Pro Ala Gly Ser Pro Leu His Trp
65 70 75

Ala Phe Thr Gln Pro Cys Ser Trp Val Ser Leu Pro Cys Lys Gln Ser
80 85 90 95

His Asn Asn Thr Arg Ile Val
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Met Arg Lys Gly Asn Leu Leu Leu Ser Trp Leu Leu Gly Pro Glu
-17 -15 -10 -5

ctt cca gag ctg tcc cca agg gct agg aag gcc gac ctg aag gat gag 154
Leu Pro Glu Leu Ser Pro Arg Ala Arg Lys Ala Asp Leu Lys Asp Glu
1 5 10

aac ctc aaa ttc agt tgc tgg tgg gag cca agg aag acg gcg ggt gtt 202
Asn Leu Lys Phe Ser Cys Trp Trp Glu Pro Arg Lys Thr Ala Gly Val
15 20 25 30

cta acg tgg ccc ttt ctg gct gag ctg gcg gaa gtg ggc gtt ttg gcc 250
Leu Thr Trp Pro Phe Leu Ala Glu Leu Ala Glu Val Gly Val Leu Ala
35 40 45

gat ggg atg tat ctc ggc gct gtg tct gtg gcc cag caa agg tgc agg 298
Asp Gly Met Tyr Leu Gly Ala Val Ser Val Ala Gln Gln Arg Cys Arg
50 55 60

gct gac tgg ctg agc cac tgg gtt cta ccc gca ggc tcc cca ctg cac 346
Ala Asp Trp Leu Ser His Trp Val Leu Pro Ala Gly Ser Pro Leu His
65 70 75

tgg gct ttc aca cag cca tgc tct tgg gtt tcc ctc cct tgt aag cag 394
Trp Ala Phe Thr Gln Pro Cys Ser Trp Val Ser Leu Pro Cys Lys Gln
80 85 90

agt cat aat aac aca cga ata gtc taacgctggg tattctggtc agcagaggtc 118
Ser His Asn Asn Thr Arg Ile Val
95 100

cttgagtcac agtgttactg aaatggttct gagcctgaga atctctttgg cctctgaaag 508
ggcagggcag gtgggcaccg acttcctgcc agtcctttca ggtttcctgt tcaaagccag 568
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<212> PRT
<213> Homo sapiens

<400> 16

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-16	-15				-10					-5					
Gln	Ser	Val	Cys	Asp	Pro	Pro	Ser	Gln	Asn	Asn	Ala	Ala	Asn	Ile	Ser
1			5				10					15			
Met	Val	Gln	Ala	Ala	Ser	Ala	Gly	Pro	Pro	Ser	Leu	Arg	Lys	Asp	Ser
			20				25					30			
Thr	Pro	Val	Ile	Ala	Asn	Val	Val	Ser	Leu	Ala	Ser	Ala	Pro	Ala	Ala
		35					40					45			
Gln	Pro	Thr	Val	Asn	Ser	Asn	Ser	Val	Leu	Gln	Gly	Ala	Val	Pro	Thr
	50					55					60				
Val	Thr	Ala	Lys	Ile	Ile	Gly	Asp	Ala	Ser	Thr	Gln	Thr	Asp	Ala	Leu
65					70					75					80
Lys	Leu	Pro	Pro	Ser	Gln	Pro	Pro	Arg	Leu	Leu	Lys	Asn	Lys	Ala	Leu
				85					90					95	
Leu	Cys	Lys	Pro	Ile	Thr	Gln	Thr	Lys	Ala	Thr	Ser	Cys	Lys	Pro	His
			100					105					110		
Thr	Gln	Asn	Lys	Glu	Cys	Gln	Thr	Glu	Asp	Thr	Pro	Ser	Gln	Pro	Gln
		115					120					125			
Ile	Ile	Val	Val	Pro	Val	Pro	Val	Pro	Val	Phe	Val	Pro	Ile	Pro	Leu
	130					135					140				
His	Leu	Tyr	Thr	Gln	Tyr	Ala	Pro	Val	Pro	Phe	Gly	Ile	Pro	Val	Pro
145					150					155					160

Met Pro Val Pro Met Leu Ile Pro Ser Ser Met Asp Ser Glu Asp Lys
165 170 175
Val Thr Glu Ser Ile Glu Asp Ile Lys Glu Lys Leu Pro Thr His Pro
180 185 190
Phe Glu Ala Asp Leu Leu Glu Met Ala Glu Met Ile Ala Glu Asp Glu
195 200 205
Glu Lys Lys Thr Leu Ser Gln Gly Glu Ser Gln Thr Ser Glu His Glu
210 215 220
Leu Phe Leu Asp Thr Lys Ile Phe Glu Lys Asp Gln Gly Ser Thr Tyr
225 230 235 240
Ser Gly Asp Leu Glu Ser Glu Ala Val Ser Thr Leu His Ser Trp Glu
245 250 255
Glu Glu Leu Asn His Tyr Ala Leu Lys Ser Asn Ala Val Gln Glu Ala
260 265 270
Asp Ser Glu Leu Lys Gln Phe Ser Lys Gly Glu Thr Glu Gln Asp Leu
275 280 285
Glu Ala Asp Phe Pro Ser Asp Ser Phe Asp Pro Leu Asn Lys Gly Gln
290 295 300
Gly Ile Gln Ala Arg Ser Arg Thr Arg Arg Arg His Arg Asp Gly Phe
305 310 315 320
Pro Gln Pro Arg Arg Arg Gly Arg Lys Lys Ser Ile Val Ala Val Glu
325 330 335
Pro Arg Ser Leu Ile Gln Gly Ala Phe Gln Gly Cys Ser Val Ser Gly
340 345 350
Met Thr Leu Lys Tyr Met Tyr Gly Val Asn Ala Trp Lys Asn Trp Val
355 360 365
Gln Trp Lys Asn Ala Lys Glu Glu Gln Gly Asp Leu Lys Cys Gly Gly
370 375 380
Val Glu Gln Ala Ser Ser Ser Pro Arg Ser Asp Pro Leu Gly Ser Thr
385 390 395 400
Gln Asp His Ala Leu Ser Gln Glu Ser Ser Glu Pro Gly Cys Arg Val
405 410 415
Arg Ser Ile Lys Leu Lys Glu Asp Ile Leu Ser Cys Thr Phe Ala Glu
420 425 430
Leu Ser Leu Gly Leu Cys Gln Phe Ile Gln Glu Val Arg Arg Pro Asn
435 440 445

Gly Glu Lys Tyr Asp Pro Asp Ser Ile Leu Tyr Leu Cys Leu Gly Ile
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Gln Gln Tyr Leu Phe Glu Asn Gly Arg Ile Asp Asn Ile Phe Thr Glu
465 470 475 480

Pro Tyr Ser Arg Phe Met Ile Glu Leu Thr Lys Leu Leu Lys Ile Trp
485 490 495

Glu Pro Thr Ile Leu Pro Asn Gly Tyr Met Phe Ser Arg Ile Glu Glu
500 505 510

Glu His Leu Trp Glu Cys Lys Gln Leu Gly Ala Tyr Ser Pro Ile Val
515 520 525

Leu Leu Asn Thr Leu Leu Phe Phe Asn Thr Lys Tyr Phe Gln Leu Lys
530 535 540

Asn Val Thr Glu His Leu Lys Leu Ser Phe Ala His Val Met Arg Arg
545 550 555 560

Thr Arg Thr Leu Lys Tyr Ser Thr Lys Met Thr Tyr Leu Arg Phe Phe
565 570 575

Pro Pro Leu Gln Lys Gln Glu Ser Glu Pro Asp Lys Leu Thr Val Gly
580 585 590

Lys Arg Lys Arg Asn Glu Asp Asp Glu Val Pro Val Gly Val Glu Met
595 600 605

Ala Glu Asn Thr Asp Asn Pro Leu Arg Cys Pro Val Arg Leu Tyr Glu
610 615 620

Phe Tyr Leu Ser Lys Cys Ser Glu Ser Val Lys Gln Arg Asn Asp Val
625 630 635 640

Phe Tyr Leu Gln Pro Glu Arg Ser Cys Val Pro Asn Ser Pro Met Trp
645 650 655

Tyr Ser Ala Phe Pro Ile Asp Pro Gly Thr Leu Asp Thr Met Leu Thr
660 665 670

Arg Ile Leu Met Val Arg Glu Val His Glu Glu Leu Ala Lys Ala Lys
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Ser Glu Asp Ser Asp Val Glu Leu Ser Asp
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<212> DNA

<213> Homo sapiens

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cacctttata ctcaatatgc tccagtccca tttggaattc cagttccaat gcctgtccct 540
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-16 -15 -10 -5

aat cag caa agt gta tgt gac ccg cct tca caa aat aat gca gca aat 95
Asn Gln Gln Ser Val Cys Asp Pro Pro Ser Gln Asn Asn Ala Ala Asn
1 5 10

att tcc atg gtt caa gct gct tca gca gga ccc cca tct ctg aga aaa 143
Ile Ser Met Val Gln Ala Ala Ser Ala Gly Pro Pro Ser Leu Arg Lys
15 20 25 30

gat tcg act cca gtt ata gcc aat gta gta tca ttg gca agt gcc cct 191
Asp Ser Thr Pro Val Ile Ala Asn Val Val Ser Leu Ala Ser Ala Pro
35 40 45

gct gct cag cct aca gtg aat tct aac agt gtc tta caa ggt gca gtt 239
Ala Ala Gln Pro Thr Val Asn Ser Asn Ser Val Leu Gln Gly Ala Val

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                50                  55                  60
cca aca gta aca gcg aaa atc atc ggt gat gca agt act caa aca gat   287
Pro Thr Val Thr Ala Lys Ile Ile Gly Asp Ala Ser Thr Gln Thr Asp
        65                  70                  75
gcc ctg aaa ctg cca cct tcc caa cct cca agg ctt ttg aag aac aaa   335
Ala Leu Lys Leu Pro Pro Ser Gln Pro Pro Arg Leu Leu Lys Asn Lys
    80                  85                  90
gct tta tta tgc aaa ccc atc aca cag act aaa gcc acc tct tgc aaa   383
Ala Leu Leu Cys Lys Pro Ile Thr Gln Thr Lys Ala Thr Ser Cys Lys
95                  100                 105                 110
cca cat acc caa aac aaa gaa tgc cag aca gaa gac act cca agt cag   431
Pro His Thr Gln Asn Lys Glu Cys Gln Thr Glu Asp Thr Pro Ser Gln
                115                 120                 125
ccc cag att att gtg gtg cca gtt ccc gta cca gtg ttt gtt ccc ata   479
Pro Gln Ile Ile Val Val Pro Val Pro Val Pro Val Phe Val Pro Ile
            130                 135                 140
cct ctt cac ctt tat act caa tat gct cca gtc cca ttt gga att cca   527
Pro Leu His Leu Tyr Thr Gln Tyr Ala Pro Val Pro Phe Gly Ile Pro
        145                 150                 155
gtt cca atg cct gtc cct atg ctt att cca tct tca atg gat agt gaa   575
Val Pro Met Pro Val Pro Met Leu Ile Pro Ser Ser Met Asp Ser Glu
    160                 165                 170
gat aaa gtc aca gag agt att gaa gac att aaa gaa aag ctt ccc aca   623
Asp Lys Val Thr Glu Ser Ile Glu Asp Ile Lys Glu Lys Leu Pro Thr
175                 180                 185                 190
cat cca ttt gaa gct gat ctc ctt gag atg gca gaa atg att gca gaa   671
His Pro Phe Glu Ala Asp Leu Leu Glu Met Ala Glu Met Ile Ala Glu
                195                 200                 205
gat gaa gag aag aag act cta tct cag gga gag tcc caa act tct gaa   719
Asp Glu Glu Lys Lys Thr Leu Ser Gln Gly Glu Ser Gln Thr Ser Glu
            210                 215                 220
cac gaa ctc ttt cta gac acc aag ata ttt gaa aaa gac caa gga agt   767
His Glu Leu Phe Leu Asp Thr Lys Ile Phe Glu Lys Asp Gln Gly Ser
        225                 230                 235
aca tac agt ggt gat ctt gaa tca gag gca gta tct act cta cat agc   815
Thr Tyr Ser Gly Asp Leu Glu Ser Glu Ala Val Ser Thr Leu His Ser
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    240                 245                 250
tgg gag gaa gag ctg aat cac tat gcc tta aag tca aat gct gtg caa    863
Trp Glu Glu Glu Leu Asn His Tyr Ala Leu Lys Ser Asn Ala Val Gln
255                 260                 265                 270
gag gct gat tca gaa ttg aag cag ttc tca aaa ggg gaa act gaa cag    911
Glu Ala Asp Ser Glu Leu Lys Gln Phe Ser Lys Gly Glu Thr Glu Gln
                275                 280                 285
gac ctg gaa gca gat ttt cca tca gac tcc ttt gac cca ctt aat aaa    959
Asp Leu Glu Ala Asp Phe Pro Ser Asp Ser Phe Asp Pro Leu Asn Lys
            290                 295                 300
gga cag gga atc cag gca cgt tcc cga aca aga cga cga cac aga gat   1007
Gly Gln Gly Ile Gln Ala Arg Ser Arg Thr Arg Arg Arg His Arg Asp
        305                 310                 315
ggc ttc ccc caa ccc aga cga aga gga cgg aag aag tct ata gtg gct   1055
Gly Phe Pro Gln Pro Arg Arg Arg Gly Arg Lys Lys Ser Ile Val Ala
    320                 325                 330
gtg gag ccc agg agt ctt att caa gga gcc ttt caa ggc tgc tca gtg   1103
Val Glu Pro Arg Ser Leu Ile Gln Gly Ala Phe Gln Gly Cys Ser Val
335                 340                 345                 350
tcc ggg atg aca ctg aaa tac atg tat ggg gta aat gct tgg aag aac   1151
Ser Gly Met Thr Leu Lys Tyr Met Tyr Gly Val Asn Ala Trp Lys Asn
                355                 360                 365
tgg gtt cag tgg aaa aat gcc aag gaa gag cag ggg gat cta aaa tgt   1199
Trp Val Gln Trp Lys Asn Ala Lys Glu Glu Gln Gly Asp Leu Lys Cys
            370                 375                 380
gga ggg gtt gaa cag gcc tca tct agc cca cgt tct gac ccc tta gga   1247
Gly Gly Val Glu Gln Ala Ser Ser Ser Pro Arg Ser Asp Pro Leu Gly
        385                 390                 395
agt act caa gac cat gca ctc tct caa gaa tcc tca gag cca ggc tgt   1295
Ser Thr Gln Asp His Ala Leu Ser Gln Glu Ser Ser Glu Pro Gly Cys
    400                 405                 410
aga gtc cgc tct atc aag ctg aag gaa gac att ctg tcc tgc act ttt   1343
Arg Val Arg Ser Ile Lys Leu Lys Glu Asp Ile Leu Ser Cys Thr Phe
415                 420                 425                 430
gct gag ttg agt ttg ggc tta tgc cag ttt atc caa gag gtg cgg aga   1391
Ala Glu Leu Ser Leu Gly Leu Cys Gln Phe Ile Gln Glu Val Arg Arg
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                435                 440                 445
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            450                 455                 460
gga att caa cag tac ctg ttt gaa aat ggt aga ata gat aac att ttt  1487
Gly Ile Gln Gln Tyr Leu Phe Glu Asn Gly Arg Ile Asp Asn Ile Phe
        465                 470                 475
act gag ccc tat tcc aga ttt atg att gaa ctt acc aaa ctc ttg aaa  1535
Thr Glu Pro Tyr Ser Arg Phe Met Ile Glu Leu Thr Lys Leu Leu Lys
    480                 485                 490
ata tgg gaa cct aca ata ctt cct aat ggt tac atg ttc tct cgc att  1583
Ile Trp Glu Pro Thr Ile Leu Pro Asn Gly Tyr Met Phe Ser Arg Ile
495                 500                 505                 510
gag gaa gag cat ttg tgg gag tgc aaa cag ctg ggc gct tac tca cca  1631
Glu Glu Glu His Leu Trp Glu Cys Lys Gln Leu Gly Ala Tyr Ser Pro
                515                 520                 525
atc gtc ctt tta aac acc ctc ctt ttc ttc aat acc aaa tac ttc caa  1679
Ile Val Leu Leu Asn Thr Leu Leu Phe Phe Asn Thr Lys Tyr Phe Gln
            530                 535                 540
cta aag aat gtt act gag cac ttg aag ctt tcc ttt gcc cat gtg atg  1727
Leu Lys Asn Val Thr Glu His Leu Lys Leu Ser Phe Ala His Val Met
        545                 550                 555
aga cgg acc agg act ctg aag tac agt acc aag atg aca tat ctg agg  1775
Arg Arg Thr Arg Thr Leu Lys Tyr Ser Thr Lys Met Thr Tyr Leu Arg
    560                 565                 570
ttc ttc cca cct tta cag aag cag gag tca gaa cca gat aaa ctg act  1823
Phe Phe Pro Pro Leu Gln Lys Gln Glu Ser Glu Pro Asp Lys Leu Thr
575                 580                 585                 590
gtt ggc aag agg aaa cga aat gaa gat gat gag gtt cca gtg ggg gtg  1871
Val Gly Lys Arg Lys Arg Asn Glu Asp Asp Glu Val Pro Val Gly Val
                595                 600                 605
gag atg gca gag aat act gac aat cca cta aga tgc cca gtc cga ctt  1919
Glu Met Ala Glu Asn Thr Asp Asn Pro Leu Arg Cys Pro Val Arg Leu
            610                 615                 620
tat gag ttt tac ctg tca aaa tgt tct gaa agt gtg aag caa agg aat  1967
Tyr Glu Phe Tyr Leu Ser Lys Cys Ser Glu Ser Val Lys Gln Arg Asn
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625 630 635

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Asp Val Phe Tyr Leu Gln Pro Glu Arg Ser Cys Val Pro Asn Ser Pro
640 645 650

atg tgg tac tcc gca ttc ccg ata gac cct gga acc ctg gac acc atg 2063
Met Trp Tyr Ser Ala Phe Pro Ile Asp Pro Gly Thr Leu Asp Thr Met
655 660 665 670

tta aca cgt att ctc atg gtg agg gag gta cat gaa gaa ctt gcc aaa 2111
Leu Thr Arg Ile Leu Met Val Arg Glu Val His Glu Glu Leu Ala Lys
675 680 685

gcc aaa tct gaa gac tct gat gtt gaa tta tca gat taaaacggaa 2157
Ala Lys Ser Glu Asp Ser Asp Val Glu Leu Ser Asp
690 695

gtgaggttct tattttcata catattggta tgcaccaaac tgtgaatgca tccagctgtt 2217
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gacttgtgaa ccccacagtg tggatgtgca aatgaaaatt gaaggaaaga atatgaactg 2337
agaaatgttc tttggcagtg atatagttct tagacatctt cagaatgact aatttctccg 2397
agtggtgcat aatcttattt tgtttgggag taacaaatcg tggaatattt ttaaggaaaa 2457
ctgttgtata aaactttacc atagtaacct tagaccttag agaggtagct ttggagtgaa 2517
actttggctg caataggcta ctttggcaag ccctccgtaa aagtcagagg agagatcagt 2577
acagagctaa gagtgacatc aaatgaggac tgtgggaccc agatttgaag acccaataaa 2637
aatactcaac tttttaaaaa aaaaa 2662

<210> 19
<211> 81
<212> PRT
<213> Homo sapiens

<400> 19
Met Arg Thr Tyr His Tyr Ile Pro Leu Phe Ile Trp Thr Tyr Met Phe
-24 -20 -15 -10
His Thr Val Asp Thr Ile Leu Leu Gln Glu Lys Pro Asn Ser Tyr Leu
-5 1 5
Ser Ser Lys Lys Ile Ala Gly Leu Thr Lys Asp Asp Gly Lys Met Leu
10 15 20
Arg Arg Thr Lys Arg Gly Trp Met Trp Asn Gln Phe Phe Leu Leu Glu

25 30 35 40

Glu Tyr Thr Gly Thr Asp Thr Gln Tyr Val Gly Lys Val Arg Ile Phe

45 50 55

Val

<210> 20
<211> 243
<212> DNA
<213> Homo sapiens

<400> 20
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accatcctat tacaagaaaa acctaacagt tatttatcaa gcaaaaagat agcgggtctg 120
acaaaagatg acggtaaaat gctacgtcgc accaagcgtg gctggatgtg gaatcagttc 180
ttcttattgg aagagtacac aggtactgac acacaatatg taggcaaggt aagaattttt 240
gta 243

<210> 21
<211> 630
<212> DNA
<213> Homo sapiens

<200>
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<222> (160)..(402)

<200>
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<222> (160)..(231)

<200>
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<222> (232)..(402)

<400> 21
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ggaactgtca gtgcggagta gggctaaact cagttccatt gttaagcaag gaaaaacaaa 120
caatacattg aatttgacaa cccactgaag ttgcagata atg agg act tac cat 171
Met Arg Thr Tyr His
-24 -20
tat ata cca tta ttc atc tgg acc tat atg ttc cat aca gtt gac acc 222
Tyr Ile Pro Leu Phe Ile Trp Thr Tyr Met Phe His Thr Val Asp Thr
-15 -10 -5
atc cta tta caa gaa aaa cct aac agt tat tta tca agc aaa aag ata 270
Ile Leu Leu Gln Glu Lys Pro Asn Ser Tyr Leu Ser Ser Lys Lys Ile
1 5 10
gcg ggt ctg aca aaa gat gac ggt aaa atg cta cgt cgc acc aag cgt 318
Ala Gly Leu Thr Lys Asp Asp Gly Lys Met Leu Arg Arg Thr Lys Arg
15 20 25
ggc tgg atg tgg aat cag ttc ttc tta ttg gaa gag tac aca ggt act 366
Gly Trp Met Trp Asn Gln Phe Phe Leu Leu Glu Glu Tyr Thr Gly Thr
30 35 40 45
gac aca caa tat gta ggc aag gta aga att ttt gta tgagaaatct 412
Asp Thr Gln Tyr Val Gly Lys Val Arg Ile Phe Val
50 55
aaaagctgaa agtgacagct atttatttt ttccagcaac ttttcttttc actagtgatt 472
attaaaaaat atttaactaa ttatgttctg aaggtgtgat attgcaaact attttagtgg 532
ggaagaacaa ggaaccatat ttgggttcta aatgtaaatc aatgtcaata ataagcgtaa 592
gctactaagt catatgtgga tggatgtgat cattatta 630

<210> 22
<211> 150
<212> PRT
<213> Homo sapiens

<400> 22
Met Arg Lys Thr Arg Leu Trp Gly Leu Leu Trp Met Leu Phe Val Ser
-20 -15 -10 -5
Glu Leu Arg Ala Ala Thr Lys Leu Thr Glu Glu Lys Tyr Glu Leu Lys
1 5 10
Glu Gly Gln Thr Leu Asp Val Lys Cys Asp Tyr Thr Leu Glu Lys Phe
15 20 25

Ala Ser Ser Gln Lys Ala Trp Gln Ile Ile Arg Asp Gly Glu Met Pro
30 35 40

Lys Thr Leu Ala Cys Thr Glu Arg Pro Ser Lys Asn Ser His Pro Val
45 50 55 60

Gln Val Gly Arg Ile Ile Leu Glu Asp Tyr His Asp His Gly Leu Leu
65 70 75

Arg Val Arg Met Val Asn Leu Gln Val Glu Asp Ser Gly Leu Tyr Gln
80 85 90

Cys Val Ile Tyr Gln Pro Pro Lys Glu Pro His Met Leu Phe Asp Arg
95 100 105

Ile Arg Leu Val Val Thr Lys Gly Phe Arg Cys Ser Thr Leu Ser Phe
110 115 120

Ser Trp Leu Val Asp Ser
125 130

<210> 23
<211> 450
<212> DNA
<213> Homo sapiens

<400> 23
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gcaactaaat taactgagga aaagtatgaa ctgaaagagg ggcagaccct ggatgtgaaa 120
tgtgactaca cgctagagaa gtttgccagc agccagaaag cttggcagat aataagggac 180
ggagagatgc ccaagaccct ggcatgcaca gagaggcctt caaagaattc ccatccagtc 240
caagtggggg ggatcatact agaagactac catgatcatg gtttactgcg cgtccgaatg 300
gtcaaccttc aagtggaaga tttctggact tatcagtgtg tgatctacca gcctcccaag 360
gagcctcaca tgctgttcga tcgcatccgc ttggtggtga ccaaggggtt ccggtgttca 420
acattgtcat tctcctggct ggtggatttc 450

<210> 24
<211> 701
<212> DNA
<213> Homo sapiens

<200>

<221> CDS
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<200>
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<222> (19)..(78)

<200>
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<222> (79)..(468)

<400> 24

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                  Met Arg Lys Thr Arg Leu Trp Gly Leu Leu Trp
                  -20                 -15                 -10

atg ctc ttt gtc tca gaa ctc cga gct gca act aaa tta act gag gaa      99
Met Leu Phe Val Ser Glu Leu Arg Ala Ala Thr Lys Leu Thr Glu Glu
              -5                  1               5

aag tat gaa ctg aaa gag ggg cag acc ctg gat gtg aaa tgt gac tac     147
Lys Tyr Glu Leu Lys Glu Gly Gln Thr Leu Asp Val Lys Cys Asp Tyr
      10                  15                  20

acg cta gag aag ttt gcc agc agc cag aaa gct tgg cag ata ata agg     195
Thr Leu Glu Lys Phe Ala Ser Ser Gln Lys Ala Trp Gln Ile Ile Arg
  25                  30                  35

gac gga gag atg ccc aag acc ctg gca tgc aca gag agg cct tca aag     243
Asp Gly Glu Met Pro Lys Thr Leu Ala Cys Thr Glu Arg Pro Ser Lys
40                  45                  50                  55

aat tcc cat cca gtc caa gtg ggg agg atc ata cta gaa gac tac cat     291
Asn Ser His Pro Val Gln Val Gly Arg Ile Ile Leu Glu Asp Tyr His
                  60                  65                  70

gat cat ggt tta ctg cgc gtc cga atg gtc aac ctt caa gtg gaa gat     339
Asp His Gly Leu Leu Arg Val Arg Met Val Asn Leu Gln Val Glu Asp
              75                  80                  85

tct gga ctg tat cag tgt gtg atc tac cag cct ccc aag gag cct cac     387
Ser Gly Leu Tyr Gln Cys Val Ile Tyr Gln Pro Pro Lys Glu Pro His
      90                  95                  100
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atg ctg ttc gat cgc atc cgc ttg gtg gtg acc aag ggg ttc cgg tgt 435
Met Leu Phe Asp Arg Ile Arg Leu Val Val Thr Lys Gly Phe Arg Cys
105 110 115

tca aca ttg tca ttc tcc tgg ctg gtg gat tcc tgagtaagag cctggtcttc 488
Ser Thr Leu Ser Phe Ser Trp Leu Val Asp Ser
120 125 130

tctgtcctgt ttgctgtcac gctgaggtca tttgtaccct aggcccacga acccacgaga 548

atgtcctctg acttccagcc acatccatct ggcagttgtg ccaagggagg agggaggagg 608

taaaaggcag ggagttaata acatgaatta aatctgtaat caccagctaa agaaaaaaaa 668

aaaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 701

<210> 25

<211> 422

<212> PRT

<213> Homo sapiens

<400> 25

Met Leu Gln Trp Arg Arg Arg His Cys Cys Phe Ala Lys Met Thr Trp
-38 -35 -30 -25

Asn Ala Lys Arg Ser Leu Phe Arg Thr His Leu Ile Gly Val Leu Ser
-20 -15 -10

Leu Val Phe Leu Phe Ala Met Phe Leu Phe Phe Asn His His Asp Trp
-5 1 5 10

Leu Pro Gly Arg Ala Gly Phe Lys Glu Asn Pro Val Thr Tyr Thr Phe
15 20 25

Arg Gly Phe Arg Ser Thr Lys Ser Glu Thr Asn His Ser Ser Leu Arg
30 35 40

Asn Ile Trp Lys Glu Thr Val Pro Gln Thr Leu Arg Pro Gln Thr Ala
45 50 55

Thr Asn Ser Asn Asn Thr Asp Leu Ser Pro Gln Gly Val Thr Gly Leu
60 65 70

Glu Asn Thr Leu Ser Ala Asn Gly Ser Ile Tyr Asn Glu Lys Gly Thr
75 80 85 90

Gly His Pro Asn Ser Tyr His Phe Lys Tyr Ile Ile Asn Glu Pro Glu
95 100 105

Lys Cys Gln Glu Lys Ser Pro Phe Leu Ile Leu Leu Ile Ala Ala Glu

110 115 120

Pro Gly Gln Ile Glu Ala Arg Arg Ala Ile Arg Gln Thr Trp Gly Asn

125 130 135

Glu Ser Leu Ala Pro Gly Ile Gln Ile Thr Arg Ile Phe Leu Leu Gly

140 145 150

Leu Ser Ile Lys Leu Asn Gly Tyr Leu Gln Arg Ala Ile Leu Glu Glu

155 160 165 170

Ser Arg Gln Tyr His Asp Ile Ile Gln Gln Glu Tyr Leu Asp Thr Tyr

175 180 185

Tyr Asn Leu Thr Ile Lys Thr Leu Met Gly Met Asn Trp Val Ala Thr

190 195 200

Tyr Cys Pro His Ile Pro Tyr Val Met Lys Thr Asp Ser Asp Met Phe

205 210 215

Val Asn Thr Glu Tyr Leu Ile Asn Lys Leu Leu Lys Pro Asp Leu Pro

220 225 230

Pro Arg His Asn Tyr Phe Thr Gly Tyr Leu Met Arg Gly Tyr Ala Pro

235 240 245 250

Asn Arg Asn Lys Asp Ser Lys Trp Tyr Met Pro Pro Asp Leu Tyr Pro

255 260 265

Ser Glu Arg Tyr Pro Val Phe Cys Ser Gly Thr Gly Tyr Val Phe Ser

270 275 280

Gly Asp Leu Ala Glu Lys Ile Phe Lys Val Ser Leu Gly Ile Arg Arg

285 290 295

Leu His Leu Glu Asp Val Tyr Val Gly Ile Cys Leu Ala Lys Leu Arg

300 305 310

Ile Asp Pro Val Pro Pro Pro Asn Glu Phe Val Phe Asn His Trp Arg

315 320 325 330

Val Ser Tyr Ser Ser Cys Lys Tyr Ser His Leu Ile Thr Ser His Gln

335 340 345

Phe Gln Pro Ser Glu Leu Ile Lys Tyr Trp Asn His Leu Gln Gln Asn

350 355 360

Lys His Asn Ala Cys Ala Asn Ala Ala Lys Glu Lys Ala Gly Arg Tyr

365 370 375

Arg His Arg Lys Leu His

380

<210> 26

<211> 1266

<212> DNA

<213> Homo sapiens

<400> 26

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tctctgttcc gcactcatct tattggagta ctttctctag tgtttctttt tgctatgttt 120

ttgtttttca atcatcatga ctggctgcca ggcagagctg gattcaaaga aaaccctgtg 180

acatacactt tccgaggatt tcggtcaaca aaaagtgaga caaaccacag ctcccttcgg 240

aacatttgga aagaaacagt ccctcaaacc ctgaggcctc aaacagcaac taactctaat 300

aacacagacc tgtcaccaca aggagttaca ggcctggaga atacacttag tgccaatgga 360

agtatttaca atgaaaaagg tactggacat ccaaattctt accatttcaa atatattatt 420

aatgagcctg aaaaatgcca agagaaaagt ccttttttaa tactactaat agctgcagag 480

cctggacaaa tagaagctag aagagctatt cggcaaactt ggggcaatga aagtctagca 540

cctggtattc aaatcacaag aatatttttg ttgggcttaa gtattaagct aaatggctac 600

cttcaacgtg caatactgga agaaagcaga caatatcatg atataattca acaggaatac 660

ttagatacgt actataattt gaccattaaa acactaatgg gcatgaactg ggttgcaaca 720

tactgtccac atattccata tgttatgaaa actgacagtg acatgtttgt caacactgaa 780

tatttaatca ataagttact gaagccagat ctgcctccca gacataacta tttcactggt 840

tacctaatgc gaggatatgc acccaatcga aacaaagata gcaagtggta catgccacca 900

gacctctacc caagtgagcg ttatcctgtc tictgttctg gaactggtta tgttttttct 960

ggagatctgg cagaaaagat ttttaaagtt tctttaggta tccgccgttt gcactiggaa 1020

gatgtataig tagggatctg tcttgccaag ttgagaattg atcctgtacc ccctcccaat 1080

gagtttgtgt tcaatcactg gcgagtctct tattcgagct gtaaatacag ccacctaatt 1140

acctctcatc agttccagcc tagtgaactg ataaaatact ggaaccattt acaacaaaat 1200

aagcacaatg cctgtgccaa cgcagcnaaa gnaaaggcag gcaggtatcg ccaccgtaaa 1260

ctacat 1266

<210> 27

<211> 2420

<212> DNA

<213> Homo sapiens

<200>

<221> CDS

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<200>
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<222> (812)..(1963)

<400> 27

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cttttccaat acaactgaag cactacattt tagctctggc tgctttacat tgcagctcag  180
tgttattagt agaaatatgg atactgagac gagaacacag cactgcattg tccagccagg  240
aaaatagcag atgtaaaaag cttcaatgca tcaactgtcg ggaagagtca acagtgctac  300
aagcagaacg ggcaactaca gctcttttgt ttaacgaaag agagaaaatg aaagaaaggg  360
aaaatttcag aagactagga cccatatgaa caaggagggt aactcgaaga caagcagaca  420
gatggacact ttggatactg tgaaaagcaa tcgcaggagg cagactgttg ggggatgtgc  480
gcatgttcga tagcatcttt tttgctgaag tgatggcgtg ccaaaagtat tttcagtggg  540
cataatcctc ttcacataaa tggcctgacc aaggaagaat gactacaaga gagacaatgt  600
gactgaatta gaaaatgatt gccaaagaat agtattaagg agaagaaaac attttiggtc  660
accaatctct catataccac tactggatat ttacaac atg ctt cag tgg agg aga    715
                                    Met Leu Gln Trp Arg Arg
                                    -38         -35
aga cac tgc tgc ttt gca aag atg acc tgg aat gcc aaa agg tct ctg      763
Arg His Cys Cys Phe Ala Lys Met Thr Trp Asn Ala Lys Arg Ser Leu
    -30             -25             -20
ttc cgc act cat ctt att gga gta ctt tct cta gtg ttt ctt ttt gct     811
Phe Arg Thr His Leu Ile Gly Val Leu Ser Leu Val Phe Leu Phe Ala
-15             -10             -5
atg ttt ttg ttt ttc aat cat cat gac tgg ctg cca ggc aga gct gga     859
Met Phe Leu Phe Phe Asn His His Asp Trp Leu Pro Gly Arg Ala Gly
 1           5              10              15
ttc aaa gaa aac cct gtg aca tac act ttc cga gga ttt cgg tca aca     907
Phe Lys Glu Asn Pro Val Thr Tyr Thr Phe Arg Gly Phe Arg Ser Thr
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                  20                  25                  30
aaa agt gag aca aac cac agc tcc ctt cgg aac att tgg aaa gaa aca   955
Lys Ser Glu Thr Asn His Ser Ser Leu Arg Asn Ile Trp Lys Glu Thr
              35                  40                  45
gtc cct caa acc ctg agg cct caa aca gca act aac tct aat aac aca  1003
Val Pro Gln Thr Leu Arg Pro Gln Thr Ala Thr Asn Ser Asn Asn Thr
          50                  55                  60
gac ctg tca cca caa gga gtt aca ggc ctg gag aat aca ctt agt gcc  1051
Asp Leu Ser Pro Gln Gly Val Thr Gly Leu Glu Asn Thr Leu Ser Ala
      65                  70                  75                  80
aat gga agt att tac aat gaa aaa ggt act gga cat cca aat tct tac  1099
Asn Gly Ser Ile Tyr Asn Glu Lys Gly Thr Gly His Pro Asn Ser Tyr
                  85                  90                  95
cat ttc aaa tat att att aat gag cct gaa aaa tgc caa gag aaa agt  1147
His Phe Lys Tyr Ile Ile Asn Glu Pro Glu Lys Cys Gln Glu Lys Ser
             100                 105                 110
cct ttt tta ata cta cta ata gct gca gag cct gga caa ata gaa gct  1195
Pro Phe Leu Ile Leu Leu Ile Ala Ala Glu Pro Gly Gln Ile Glu Ala
         115                 120                 125
aga aga gct att cgg caa act tgg ggc aat gaa agt cta gca cct ggt  1243
Arg Arg Ala Ile Arg Gln Thr Trp Gly Asn Glu Ser Leu Ala Pro Gly
     130                 135                 140
att caa atc aca aga ata ttt ttg ttg ggc tta agt att aag cta aat  1291
Ile Gln Ile Thr Arg Ile Phe Leu Leu Gly Leu Ser Ile Lys Leu Asn
145                 150                 155                 160
ggc tac ctt caa cgt gca ata ctg gaa gaa agc aga caa tat cat gat  1339
Gly Tyr Leu Gln Arg Ala Ile Leu Glu Glu Ser Arg Gln Tyr His Asp
                165                 170                 175
ata att caa cag gaa tac tta gat acg tac tat aat ttg acc att aaa  1387
Ile Ile Gln Gln Glu Tyr Leu Asp Thr Tyr Tyr Asn Leu Thr Ile Lys
            180                 185                 190
aca cta atg ggc atg aac tgg gtt gca aca tac tgt cca cat att cca  1435
Thr Leu Met Gly Met Asn Trp Val Ala Thr Tyr Cys Pro His Ile Pro
        195                 200                 205
tat gtt atg aaa act gac agt gac atg ttt gtc aac act gaa tat tta  1483
Tyr Val Met Lys Thr Asp Ser Asp Met Phe Val Asn Thr Glu Tyr Leu
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    210                 215                 220
atc aat aag tta ctg aag cca gat ctg cct ccc aga cat aac tat ttc  1531
Ile Asn Lys Leu Leu Lys Pro Asp Leu Pro Pro Arg His Asn Tyr Phe
225                 230                 235                 240
act ggt tac cta atg cga gga tat gca ccc aat cga aac aaa gat agc  1579
Thr Gly Tyr Leu Met Arg Gly Tyr Ala Pro Asn Arg Asn Lys Asp Ser
                245                 250                 255
aag tgg tac atg cca cca gac ctc tac cca agt gag cgt tat cct gtc  1627
Lys Trp Tyr Met Pro Pro Asp Leu Tyr Pro Ser Glu Arg Tyr Pro Val
            260                 265                 270
ttc tgt tct gga act ggt tat gtt ttt tct gga gat ctg gca gaa aag  1675
Phe Cys Ser Gly Thr Gly Tyr Val Phe Ser Gly Asp Leu Ala Glu Lys
        275                 280                 285
att ttt aaa gtt tct tta ggt atc cgc cgt ttg cac ttg gaa gat gta  1723
Ile Phe Lys Val Ser Leu Gly Ile Arg Arg Leu His Leu Glu Asp Val
    290                 295                 300
tat gta ggg atc tgt ctt gcc aag ttg aga att gat cct gta ccc cct  1771
Tyr Val Gly Ile Cys Leu Ala Lys Leu Arg Ile Asp Pro Val Pro Pro
305                 310                 315                 320
ccc aat gag ttt gtg ttc aat cac tgg cga gtc tct tat tcg agc tgt  1819
Pro Asn Glu Phe Val Phe Asn His Trp Arg Val Ser Tyr Ser Ser Cys
                325                 330                 335
aaa tac agc cac cta att acc tct cat cag ttc cag cct agt gaa ctg  1867
Lys Tyr Ser His Leu Ile Thr Ser His Gln Phe Gln Pro Ser Glu Leu
            340                 345                 350
ata aaa tac tgg aac cat tta caa caa aat aag cac aat gcc tgt gcc  1915
Ile Lys Tyr Trp Asn His Leu Gln Gln Asn Lys His Asn Ala Cys Ala
        355                 360                 365
aac gca gca aaa gaa aag gca ggc agg tat cgc cac cgt aaa cta cat  1963
Asn Ala Ala Lys Glu Lys Ala Gly Arg Tyr Arg His Arg Lys Leu His
    370                 375                 380
tagaaaagac aattttttit caaatgtgca atttgtaaat attgctaaaa gcatgtatag 2023
ttagaactga ttacatccgt aggacaagtt ttagttaaaa ctcatcacat aaagaaattc 2083
aagaagtatt ttttaatit ctgaagaagt taattcttaa aactataaca ttatattaca 2143
aaaaaggttt cccaaaacaa tctatttaaa aaactgtata aggagattct gtgtattaac 2203
atgcaattaac aagcatgcat aaatcaattgg ttcaagtctt ctgttagggg ccaataaaat 2263
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gtatctgcat atgttttcca cataaatttt aattcaagaa atgacagtca aaagatcctt 2323
cattttagat taagcttttc attttaatat ataatttaat gtaaataaaa catcactatc 2383
aattttaagg aaaaaaaaaa aaaaaaaaaa aaaaaaa 2420

<210> 28
<211> 521
<212> PRT
<213> Homo sapiens

<400> 28

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-21		-20				-15				-10					
Leu	Asp	Ala	Ser	Thr	Asp	Glu	Val	Ala	Thr	Glu	Asn	Ile	Leu	Lys	Ala
-5				1			5					10			
Glu	Leu	Thr	Met	Ala	Ala	Leu	Cys	Gly	Arg	Leu	Gly	Leu	Val	Thr	Ser
			15				20					25			
Arg	Asp	Ala	Phe	Ile	Thr	Ala	Ile	Cys	Lys	Gly	Ser	Leu	Pro	Pro	His
		30				35					40				
Tyr	Ala	Leu	Thr	Val	Leu	Asn	Thr	Thr	Thr	Ala	Ala	Thr	Leu	Ser	Asn
	45					50					55				
Lys	Ser	Tyr	Ser	Val	Gln	Gly	Gln	Ser	Val	Met	Met	Ile	Ser	Pro	Ser
60					65					70					75
Ser	Glu	Ser	His	Gln	Gln	Val	Val	Ala	Val	Gly	Gln	Pro	Leu	Ala	Val
				80					85					90	
Gln	Pro	Gln	Gly	Thr	Val	Met	Leu	Thr	Ser	Lys	Asn	Ile	Gln	Cys	Met
			95					100					105		
Arg	Thr	Leu	Leu	Asn	Leu	Ala	His	Cys	His	Gly	Ala	Val	Leu	Gly	Thr
		110					115					120			
Ser	Trp	Gln	Leu	Val	Leu	Ala	Thr	Leu	Gln	His	Leu	Val	Trp	Ile	Leu
	125					130					135				
Gly	Leu	Lys	Pro	Ser	Ser	Gly	Gly	Ala	Leu	Lys	Pro	Gly	Arg	Ala	Val
140					145					150					155
Glu	Gly	Pro	Ser	Thr	Val	Leu	Thr	Thr	Ala	Val	Met	Thr	Asp	Leu	Pro
				160					165					170	
Val	Ile	Ser	Asn	Ile	Leu	Ser	Arg	Leu	Phe	Glu	Ser	Ser	Gln	Tyr	Leu
			175					180					185		

Asp Asp Val Ser Leu His His Leu Ile Asn Ala Leu Cys Ser Leu Ser
190 195 200

Leu Glu Ala Met Asp Met Ala Tyr Gly Asn Asn Lys Glu Pro Ser Leu
205 210 215

Phe Ala Val Ala Lys Leu Leu Glu Thr Gly Leu Val Asn Met His Arg
220 225 230 235

Ile Glu Ile Leu Trp Arg Pro Leu Thr Gly His Leu Leu Glu Lys Val
240 245 250

Cys Gln His Pro Asn Ser Arg Met Gly Glu Trp Gly Ala Glu Ala Leu
255 260 265

Thr Ser Leu Ile Lys Ala Gly Leu Thr Phe Asn His Asp Pro Pro Leu
270 275 280

Ser Gln Asn Gln Arg Leu Gln Leu Leu Leu Leu Asn Pro Leu Lys Glu
285 290 295

Met Ser Asn Ile Asn His Pro Asp Ile Arg Leu Lys Gln Leu Glu Cys
300 305 310 315

Val Leu Gln Ile Leu Gln Ser Gln Gly Asp Asn Leu Gly Pro Gly Trp
320 325 330

Pro Leu Val Leu Gly Val Met Gly Ala Ile Arg Asn Asp Gln Gly Glu
335 340 345

Ser Leu Ile Arg Thr Ala Phe Gln Cys Leu Gln Leu Val Val Thr Asp
350 355 360

Phe Leu Pro Thr Met Pro Cys Thr Cys Leu Gln Ile Val Val Asp Val
365 370 375

Ala Gly Ser Phe Gly Leu His Asn Gln Glu Leu Asn Ile Ser Leu Thr
380 385 390 395

Ser Ile Gly Leu Leu Trp Asn Ile Ser Asp Tyr Phe Phe Gln Arg Gly
400 405 410

Glu Thr Ile Glu Lys Glu Leu Asn Lys Glu Glu Ala Ala Gln Gln Lys
415 420 425

Gln Ala Glu Glu Lys Gly Val Val Leu Asn Arg Pro Phe His Pro Ala
430 435 440

Pro Pro Phe Asp Cys Leu Trp Leu Cys Leu Tyr Ala Lys Leu Gly Glu
445 450 455

Leu Cys Val Asp Pro Arg Pro Ala Val Arg Lys Ser Ala Gly Gln Thr
460 465 470 475

Leu Phe Ser Thr Ile Gly Ala His Gly Thr Leu Leu Gln His Ser Thr
480 485 490

Trp Arg Thr Val Ile Trp Lys Val Leu
495 500

<210> 29
<211> 1563
<212> DNA
<213> Homo sapiens

<400> 29

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Leu Leu Leu Asp Ala Ser Thr Asp Glu Val Ala Thr Glu Asn Ile Leu
-5 1 5

aaa gct gaa ctg act atg gct gct ctt tgt gga aga ctg ggc ctt gta 145
Lys Ala Glu Leu Thr Met Ala Ala Leu Cys Gly Arg Leu Gly Leu Val
10 15 20 25

act tca aga gat gcc ttt ata act gca ata tgc aaa ggt tcc ctg cct 193
Thr Ser Arg Asp Ala Phe Ile Thr Ala Ile Cys Lys Gly Ser Leu Pro
30 35 40

ccc cat tat gct ctt act gta ttg aat acc acc act gca gct aca ctt 241
Pro His Tyr Ala Leu Thr Val Leu Asn Thr Thr Thr Ala Ala Thr Leu
45 50 55

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Ser Asn Lys Ser Tyr Ser Val Gln Gly Gln Ser Val Met Met Ile Ser
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cca tca agt gaa tct cac caa caa gtt gtg gca gtg ggt caa cct tta   337
Pro Ser Ser Glu Ser His Gln Gln Val Val Ala Val Gly Gln Pro Leu
    75                  80                  85

gca gtc cag cct caa ggg aca gta atg ctg act tcc aaa aat atc cag   385
Ala Val Gln Pro Gln Gly Thr Val Met Leu Thr Ser Lys Asn Ile Gln
90                  95                  100                 105

tgt atg agg act tta ctt aac ttg gcg cat tgc cat ggg gct gtt ctt   433
Cys Met Arg Thr Leu Leu Asn Leu Ala His Cys His Gly Ala Val Leu
                110                 115                 120

gga aca tca tgg caa ctt gtc ttg gca act ctt cag cat ctt gtg tgg   481
Gly Thr Ser Trp Gln Leu Val Leu Ala Thr Leu Gln His Leu Val Trp
            125                 130                 135

att ctg gga tta aag cct agt agt ggc ggt gcc ttg aaa cct ggg aga   529
Ile Leu Gly Leu Lys Pro Ser Ser Gly Gly Ala Leu Lys Pro Gly Arg
        140                 145                 150

gct gta gaa gga ccc agt aca gtt cta aca aca gca gtg atg aca gat   577
Ala Val Glu Gly Pro Ser Thr Val Leu Thr Thr Ala Val Met Thr Asp
    155                 160                 165

tta cca gtg att tcc aat ata ctt tca aga ttg ttt gaa agc tca cag   625
Leu Pro Val Ile Ser Asn Ile Leu Ser Arg Leu Phe Glu Ser Ser Gln
170                 175                 180                 185

tat ctt gat gat gta tca ctg cat cat tta ata aat gca ctt tgc tcc   673
Tyr Leu Asp Asp Val Ser Leu His His Leu Ile Asn Ala Leu Cys Ser
                190                 195                 200

ttg tct cta gaa gca atg gat atg gcc tat gga aat aat aag gaa cca   721
Leu Ser Leu Glu Ala Met Asp Met Ala Tyr Gly Asn Asn Lys Glu Pro
            205                 210                 215

tct ctt ttt gct gtt gcc aaa ttg tta gaa act ggt tta gtt aat atg   769
Ser Leu Phe Ala Val Ala Lys Leu Leu Glu Thr Gly Leu Val Asn Met
        220                 225                 230

cac cga ata gaa att ctg tgg aga cct ctg act ggc cat cta ctt gag   817
His Arg Ile Glu Ile Leu Trp Arg Pro Leu Thr Gly His Leu Leu Glu
    235                 240                 245
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aag gtc tgc cag cat cca aac tct cga atg gga gaa tgg gga gca gaa      865
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gct tta act tct ctt att aaa gca gga tta aca ttt aac cat gat cct      913
Ala Leu Thr Ser Leu Ile Lys Ala Gly Leu Thr Phe Asn His Asp Pro
                270                 275                 280
cca ctc tca caa aac cag agg ctg cag ttg ctt tta ttg aac ccg tta      961
Pro Leu Ser Gln Asn Gln Arg Leu Gln Leu Leu Leu Leu Asn Pro Leu
            285                 290                 295
aag gag atg tcc aat att aat cat cca gat att cga ctc aag cag tta     1009
Lys Glu Met Ser Asn Ile Asn His Pro Asp Ile Arg Leu Lys Gln Leu
        300                 305                 310
gaa tgc gtg ttg cag att ctg cag agt cag gga gac aat ctt ggg cct     1057
Glu Cys Val Leu Gln Ile Leu Gln Ser Gln Gly Asp Asn Leu Gly Pro
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330                 335                 340                 345
gga gaa tcc ttg ata cga act gca ttc cag tgt ctt cag ttg gtt gtg     1153
Gly Glu Ser Leu Ile Arg Thr Ala Phe Gln Cys Leu Gln Leu Val Val
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aca gat ttt cta cca aca atg cct tgt act tgc ctg caa ata gtt gta     1201
Thr Asp Phe Leu Pro Thr Met Pro Cys Thr Cys Leu Gln Ile Val Val
            365                 370                 375
gat gtt gca ggt agc ttt ggc ctc cat aac caa gaa ctc aat att agt     1249
Asp Val Ala Gly Ser Phe Gly Leu His Asn Gln Glu Leu Asn Ile Ser
        380                 385                 390
tta act tca atg ggt tta ttg tgg aat att tca gat tat ttt ttc caa     1297
Leu Thr Ser Ile Gly Leu Leu Trp Asn Ile Ser Asp Tyr Phe Phe Gln
    395                 400                 405
aga ggg gaa act att gaa aaa gaa cta aat aag gaa gag gca gca cag     1345
Arg Gly Glu Thr Ile Glu Lys Glu Leu Asn Lys Glu Glu Ala Ala Gln
410                 415                 420                 425
caa aag cag gca gaa gag aaa gga gtt gtt tta aat cgg cca ttc cac     1393
Gln Lys Gln Ala Glu Glu Lys Gly Val Val Leu Asn Arg Pro Phe His
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445 450 455

ggt gaa cta tgt gtg gat ccc cgt cct gct gtc agg aag agt gca ggg 1489
Gly Glu Leu Cys Val Asp Pro Arg Pro Ala Val Arg Lys Ser Ala Gly
460 465 470

caa act ctg ttt tct aca att ggt gcg cat gga act tta tta cag cat 1537
Gln Thr Leu Phe Ser Thr Ile Gly Ala His Gly Thr Leu Leu Gln His
475 480 485

tca acc tgg cgc act gtt atc tgg aag gta ttg taaaatagat tggactatca 1590
Ser Thr Trp Arg Thr Val Ile Trp Lys Val Leu
490 495 500

gcttttaatg agtcatgctt atatattaat acttttcag ttaaacttat ttcttttaat 1650

ttttaaagaa tttccatgca tttgtgtatt tgacaaaaca ggaaataact gtgtcatatt 1710

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Glu Leu Thr Met Ala Ala Leu Cys Gly Arg Leu Gly Leu Val Thr Ser
15 20 25

Arg Asp Ala Phe Ile Thr Ala Ile Cys Lys Gly Ser Leu Pro Pro His
30 35 40

Tyr Ala Leu Thr Val Leu Asn Thr Thr Thr Ala Ala Thr Leu Ser Asn
45 50 55

Lys Ser Tyr Ser Val Gln Gly Gln Ser Val Met Met Ile Ser Pro Ser
60 65 70 75

Ser Glu Ser His Gln Gln Val Val Ala Val Gly Gln Pro Leu Ala Val
80 85 90

Gln Pro Gln Gly Thr Val Met Leu Thr Ser Lys Asn Ile Gln Cys Met
95 100 105
Arg Thr Leu Leu Asn Leu Ala His Cys His Gly Ala Val Leu Gly Thr
110 115 120
Ser Trp Gln Leu Val Leu Ala Thr Leu Gln His Leu Val Trp Ile Leu
125 130 135
Gly Leu Lys Pro Ser Ser Gly Gly Ala Leu Lys Pro Gly Arg Ala Val
140 145 150 155
Glu Gly Pro Ser Thr Val Leu Thr Thr Ala Val Met Thr Asp Leu Pro
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Val Ile Ser Asn Ile Leu Ser Arg Leu Phe Glu Ser Ser Arg Tyr Leu
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Asp Asp Val Ser Leu His His Leu Ile Asn Ala Leu Cys Ser Leu Ser
190 195 200
Leu Glu Ala Met Asp Met Ala Tyr Gly Asn Asn Lys Glu Pro Ser Leu
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Phe Ala Val Ala Lys Leu Leu Glu Thr Gly Leu Val Asn Met His Arg
220 225 230 235
Ile Glu Ile Leu Trp Arg Pro Leu Thr Gly His Leu Leu Glu Val Cys
240 245 250
Gln His Pro Asn Ser Arg Met Arg Glu Trp Gly Ala Glu Ala Leu Thr
255 260 265
Ser Leu Ile Lys Ala Gly Leu Thr Phe Asn His Asp Pro Pro Leu Ser
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Gln Asn Gln Arg Leu Gln Leu Leu Leu Leu Asn Pro Leu Lys Glu Met
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Ser Asn Ile Asn His Pro Asp Ile Arg Leu Lys Gln Leu Glu Cys Val
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350 355 360
Ile Phe Val Leu Lys Ala Val Ser Thr Leu Ile Asp Ser Leu Lys Lys
365 370 375

Thr Gln Pro Glu Asn Val Asp Gly Asn Thr Trp Ala Gln Val Ile Ala
380 385 390 395
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caacaagttg tggcagtggg tcaaccttta gcagtccagc ctcaagggac agtaatgctg 360
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gttcttggaa catcatggca acttgtcttg gcaactcttc agcatcttgt gtggattctg 480
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Leu Leu Leu Asp Ala Ser Thr Asp Glu Val Ala Thr Glu Asn Ile Leu
-5 1 5

aaa gct gaa ctg act atg gct gct ctt tgt gga aga ctg ggc ctt gta 145
Lys Ala Glu Leu Thr Met Ala Ala Leu Cys Gly Arg Leu Gly Leu Val
10 15 20 25

act tca aga gat gcc ttt ata act gcn ata tgc aan ggt tcc ctg cct 193
Thr Ser Arg Asp Ala Phe Ile Thr Ala Ile Cys Lys Gly Ser Leu Pro
30 35 40

ccc cat tat gct ctt act gta ttg aat acc acc act gca gct aca ctt 241
Pro His Tyr Ala Leu Thr Val Leu Asn Thr Thr Thr Ala Ala Thr Leu
45 50 55

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tcc aac aaa tca tat tcc gtt cag ggc caa agt gtt atg atg ata agt   289
Ser Asn Lys Ser Tyr Ser Val Gln Gly Gln Ser Val Met Met Ile Ser
        60                  65                  70

cca tca agt gaa tct cac caa caa gtt gtg gca gtg ggt caa cct tta   337
Pro Ser Ser Glu Ser His Gln Gln Val Val Ala Val Gly Gln Pro Leu
    75                  80                  85

gca gtc cag cct caa ggg aca gta atg ctg act tcc aaa aat atc cag   385
Ala Val Gln Pro Gln Gly Thr Val Met Leu Thr Ser Lys Asn Ile Gln
90                  95                  100                 105

tgt atg agg act tta ctt aac ttg gcg cat tgc cat ggg gct gtt ctt   433
Cys Met Arg Thr Leu Leu Asn Leu Ala His Cys His Gly Ala Val Leu
                110                 115                 120

gga aca tca tgg caa ctt gtc ttg gca act ctt cag cat ctt gtg tgg   481
Gly Thr Ser Trp Gln Leu Val Leu Ala Thr Leu Gln His Leu Val Trp
            125                 130                 135

att ctg gga tta aag cct agt agt ggc ggt gcc ttg aaa cct ggg aga   529
Ile Leu Gly Leu Lys Pro Ser Ser Gly Gly Ala Leu Lys Pro Gly Arg
        140                 145                 150

gct gta gaa gga ccc agt aca gtt cta aca aca gca gtg atg aca gat   577
Ala Val Glu Gly Pro Ser Thr Val Leu Thr Thr Ala Val Met Thr Asp
    155                 160                 165

tta cca gtg att tcc aat ata ctt tca aga ttg ttt gaa agc tca cgg   625
Leu Pro Val Ile Ser Asn Ile Leu Ser Arg Leu Phe Glu Ser Ser Arg
170                 175                 180                 185

tat ctt gat gat gta tca ctg cat cat tta ata aat gca ctt tgc tcc   673
Tyr Leu Asp Asp Val Ser Leu His His Leu Ile Asn Ala Leu Cys Ser
                190                 195                 200

ttg tct cta gaa gca atg gat atg gcc tat gga aat aat aag gaa cca   721
Leu Ser Leu Glu Ala Met Asp Met Ala Tyr Gly Asn Asn Lys Glu Pro
            205                 210                 215

tct ctt ttt gct gtt gcc aaa ttg tta gaa act ggt tta gtt aat atg   769
Ser Leu Phe Ala Val Ala Lys Leu Leu Glu Thr Gly Leu Val Asn Met
        220                 225                 230

cac cga ata gaa att ctg tgg aga cct ctg act ggc cat cta ctt gag   817
His Arg Ile Glu Ile Leu Trp Arg Pro Leu Thr Gly His Leu Leu Glu
    235                 240                 245
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Val Cys Gln His Pro Asn Ser Arg Met Arg Glu Trp Gly Ala Glu Ala
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Leu Thr Ser Leu Ile Lys Ala Gly Leu Thr Phe Asn His Asp Pro Pro
                270                 275                 280
ctc tca caa aac cag agg ctg cag ttg ctt tta ttg aac ccg tta aag   961
Leu Ser Gln Asn Gln Arg Leu Gln Leu Leu Leu Leu Asn Pro Leu Lys
            285                 290                 295
gag atg tcc aat att aat cat cca gat att cga ctc aag cag tta gaa  1009
Glu Met Ser Asn Ile Asn His Pro Asp Ile Arg Leu Lys Gln Leu Glu
        300                 305                 310
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Cys Val Leu Gln Ile Leu Gln Ser Gln Gly Asp Ser Leu Gly Pro Gly
    315                 320                 325
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Trp Pro Leu Val Leu Gly Val Met Gly Ala Ile Arg Asn Asp Gln Gly
330                 335                 340                 345
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Glu Ser Leu Ile Arg Thr Ala Phe Gln Cys Leu Gln Leu Val Val Thr
                350                 355                 360
gaa att ata ttt gtt tta aaa gca gtc agt act ctt att gat tca ctt  1201
Glu Ile Ile Phe Val Leu Lys Ala Val Ser Thr Leu Ile Asp Ser Leu
            365                 370                 375
aag aaa act cag cct gag aat gtt gat gga aat acc tgg gca caa gta  1249
Lys Lys Thr Gln Pro Glu Asn Val Asp Gly Asn Thr Trp Ala Gln Val
        380                 385                 390
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Ile Ala Leu Tyr Pro Thr Leu Val Glu Cys Ile Ala Cys Pro Ser Ser
    395                 400                 405
gaa gtc tgt tct gca ctt aaa gag gca cta gtt cct ttt aag gat ttc  1345
Glu Val Cys Ser Ala Leu Lys Glu Ala Leu Val Pro Phe Lys Asp Phe
410                 415                 420                 425
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Val Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly
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Arg Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr
60 65 70 75
Ile Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile
80 85 90
Gln Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val
95 100 105
Ile Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Leu Gln Arg Asp Phe
110 115 120
Thr Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala

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Leu Ile Ala Lys Arg Arg Tyr Arg Ile

160

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<213> Homo sapiens

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agatactggc taaatgggga tttccgcaaa ggagatgtgt ccctgaccat agagaatgtg 300

actctagcag acagtgggat ctactgctgc cggatccaaa tcccaggcat aatgaatgat 360

gaaaaattta acctgaagtt ggtcatcaaa ccagccaagg tcaccccctgc accgactctg 420

cagagagact tcactgcagc ctttccaagg atgcttacca ccaggggaca tggcccagca 480

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<222> (53)..(115)

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<222> (116)..(607)

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Met
-21

ttt tca cat ctt ccc ttt gac tgt gtc ctg ctg ctg ctg ctg cta cta 103
Phe Ser His Leu Pro Phe Asp Cys Val Leu Leu Leu Leu Leu Leu Leu
-20 -15 -10 -5

ctt aca agg tcc tca gaa gtg gaa tac aga gcg gag gtc ggt cag aat 151
Leu Thr Arg Ser Ser Glu Val Glu Tyr Arg Ala Glu Val Gly Gln Asn
1 5 10

gcc tat ctg ccc tgc ttc tac acc cca gcc gcc cca ggg aac ctc gtg 199
Ala Tyr Leu Pro Cys Phe Tyr Thr Pro Ala Ala Pro Gly Asn Leu Val
15 20 25

ccc gtc tgc tgg ggc aaa gga gcc tgt cct gtg ttt gaa tgt ggc aac 247
Pro Val Cys Trp Gly Lys Gly Ala Cys Pro Val Phe Glu Cys Gly Asn
30 35 40

gtg gtg ctc agg act gat gaa agg gat gtg aat tat tgg aca tcc aga 295
Val Val Leu Arg Thr Asp Glu Arg Asp Val Asn Tyr Trp Thr Ser Arg
45 50 55 60

tac tgg cta aat ggg gat ttc cgc aaa gga gat gtg tcc ctg acc ata 343
Tyr Trp Leu Asn Gly Asp Phe Arg Lys Gly Asp Val Ser Leu Thr Ile
65 70 75

gag aat gtg act cta gca gac agt ggg atc tac tgc tgc cgg atc caa 391
Glu Asn Val Thr Leu Ala Asp Ser Gly Ile Tyr Cys Cys Arg Ile Gln
80 85 90

atc cca ggc ata atg aat gat gaa aaa ttt aac ctg aag ttg gtc atc 439
Ile Pro Gly Ile Met Asn Asp Glu Lys Phe Asn Leu Lys Leu Val Ile
95 100 105

aaa cca gcc aag gtc acc cct gca ccg act ctg cag aga gac ttc act 487
Lys Pro Ala Lys Val Thr Pro Ala Pro Thr Leu Gln Arg Asp Phe Thr
110 115 120

gca gcc ttt cca agg atg ctt acc acc agg gga cat ggc cca gca gag 535

Ala Ala Phe Pro Arg Met Leu Thr Thr Arg Gly His Gly Pro Ala Glu
125 130 135 140

aca cag aca ctg ggg agc ctc cct gat ata aat cta aca ggt att ctc 583
Thr Gln Thr Leu Gly Ser Leu Pro Asp Ile Asn Leu Thr Gly Ile Leu
145 150 155

ata gca aag aga aga tac aga att taagcctcat ctctttggcc aacctccctc 637
Ile Ala Lys Arg Arg Tyr Arg Ile
160

cctcaggatt ggcaaatgca gtagcagagg gaattcgctc agaagaaaac atctatacca 697
ttgaagagaa cgtatatgaa gtggaggagc ccaatgagta ttattgctat gtcagcagca 757
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aaaaaaaaaa aaaa 2091

<210> 37
<211> 98

<212> PRT

<213> Homo sapiens

<400> 37

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1 5 10 15
Lys Leu Pro Ser Leu Pro Leu Val Gln Gly Glu Leu Val Gly Gly Leu
20 25 30
Thr Cys Leu Thr Ala Gln Thr His Ser Leu Leu Gln His Gln Pro Leu
35 40 45
Gln Leu Thr Thr Leu Leu Asp Gln Tyr Ile Arg Glu Gln Arg Glu Lys
50 55 60
Asp Ser Val Met Ser Ala Asn Gly Lys Pro Asp Pro Asp Thr Val Pro
65 70 75 80
Asp Ser

<210> 38

<211> 294

<212> DNA

<213> Homo sapiens

<400> 38

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caggggggagc ttgtaggagg cctcacctgc ctcacagccc agacccactc cctgctccag 180
caccagcccc tccagctgac caccctgttg gaccagtaca tcagagagca acgcgagaag 240
gattctgtca tgtcggccaa tgggaagcca gatcctgaca ctgttccgga ctcg 294

<210> 39

<211> 1094

<212> DNA

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<400> 39

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                       Met Val Arg Ile Leu Arg Thr Val Pro Phe
                       -16 -15             -10

ctg ccg ctg cta ggt ggc tgc att gat gac acc atc ctc agc agg cag      99
Leu Pro Leu Leu Gly Gly Cys Ile Asp Asp Thr Ile Leu Ser Arg Gln
 -5                  1               5                  10

ggc ttt atc aac tac tcc aag ctc ccc agc ctg ccc ctg gtg cag ggg     147
Gly Phe Ile Asn Tyr Ser Lys Leu Pro Ser Leu Pro Leu Val Gln Gly
              15                  20                  25

gag ctt gta gga ggc ctc acc tgc ctc aca gcc cag acc cac tcc ctg     195
Glu Leu Val Gly Gly Leu Thr Cys Leu Thr Ala Gln Thr His Ser Leu
          30                  35                  40

ctc cag cac cag ccc ctc cag ctg acc acc ctg ttg gac cag tac atc     243
Leu Gln His Gln Pro Leu Gln Leu Thr Thr Leu Leu Asp Gln Tyr Ile
      45                  50                  55

aga gag caa cgc gag aag gat tct gtc atg tcg gcc aat ggg aag cca     291
Arg Glu Gln Arg Glu Lys Asp Ser Val Met Ser Ala Asn Gly Lys Pro
  60                  65                  70

gat cct gac act gtt ccg gac tcg tagccagcct gtttagccag ccctgcgcat    345
Asp Pro Asp Thr Val Pro Asp Ser
 75                  80

anatacactc tgcgttattg gctgtgctct cctcantggg acatgtggna gnacttgggg   405
tcgaggagtg tgttttgtcac ttggttttca ctagtaatga tattgtcagg tatngggcca   465
cttggagatg cagnggnttc catttcngat gtcagtcacc ggcttcgtcc ttngttttcc   525
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caacttggga cgtgatagga gcaaagtctc tccattctcc aggtccaagg cagagatcct 585
gaaaagatag ggctattgtc ccctgcctcc ttggtcactg cctcttgctg cacgggctcc 645
tgagcccacc cccttggggc acaacctgcc actgccacag tagctcaacc aagcagttgt 705
gctgagaatg gcacctggtg agagcctgct gtgtgccagg ctttgtgctg agtgctgtac 765
atgtattagt tcctttactg ctgaccacat tgtacccatt tcacagagaa ggagcagaga 825
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acccagaagt gggtcccatc caccatccag gtgtgcttgg atgttagttc tccaccctcg 1005
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aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 1094

<210> 40
<211> 474
<212> PRT
<213> Homo sapiens

<400> 40

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-23			-20				-15					-10			
Leu	Val	Trp	Leu	Ile	Asp	Cys	Ile	Lys	Ile	His	Thr	Ala	Met	Lys	Glu
		-5					1				5				
Ser	Ser	Pro	Leu	Phe	Asp	Asp	Gly	Gln	Pro	Trp	Gly	Glu	Glu	Thr	Glu
10				15					20						25
Asp	Gly	Ile	Met	His	Asn	Lys	Leu	Phe	Leu	Asp	Tyr	Thr	Ile	Lys	Cys
				30					35					40	
Tyr	Glu	Ser	Phe	Met	Ser	Gly	Ala	Asp	Ser	Phe	Asp	Glu	Met	Asn	Ala
			45					50					55		
Glu	Leu	Gln	Ser	Lys	Leu	Lys	Asp	Leu	Phe	Asn	Val	Asp	Ala	Phe	Lys
		60					65					70			
Leu	Glu	Ser	Leu	Glu	Ala	Lys	Asn	Arg	Ala	Leu	Asn	Glu	Gln	Ile	Ala
	75					80					85				
Arg	Leu	Glu	Gln	Glu	Arg	Glu	Lys	Glu	Pro	Asn	Arg	Leu	Glu	Ser	Leu
90					95					100					105
Arg	Lys	Leu	Lys	Ala	Ser	Leu	Gln	Gly	Asp	Val	Gln	Lys	Tyr	Gln	Ala
				110					115					120	
Tyr	Met	Ser	Asn	Leu	Glu	Ser	His	Ser	Ala	Ile	Leu	Asp	Gln	Lys	Leu

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                125                 130                 135
Asn Gly Leu Asn Glu Glu Ile Ala Arg Val Glu Leu Glu Cys Glu Thr
        140                 145                 150
Ile Lys Gln Glu Asn Thr Arg Leu Gln Asn Ile Ile Asp Asn Gln Lys
    155                 160                 165
Tyr Ser Val Ala Asp Ile Glu Arg Ile Asn His Glu Arg Asn Glu Leu
170                 175                 180                 185
Gln Gln Thr Ile Asn Lys Leu Thr Lys Asp Leu Glu Ala Glu Gln Gln
                190                 195                 200
Lys Leu Trp Asn Glu Glu Leu Lys Tyr Ala Arg Gly Lys Glu Ala Ile
            205                 210                 215
Glu Thr Gln Leu Ala Glu Tyr His Lys Leu Ala Arg Lys Leu Lys Leu
        220                 225                 230
Ile Pro Lys Gly Ala Glu Asn Ser Lys Gly Tyr Asp Phe Glu Ile Lys
    235                 240                 245
Phe Asn Pro Glu Ala Gly Ala Asn Cys Leu Val Lys Tyr Arg Ala Gln
250                 255                 260                 265
Val Tyr Val Pro Leu Lys Glu Leu Leu Asn Glu Thr Glu Glu Glu Ile
                270                 275                 280
Asn Lys Ala Leu Asn Lys Lys Met Gly Leu Glu Asp Thr Leu Glu Gln
            285                 290                 295
Leu Asn Ala Met Ile Thr Glu Ser Lys Arg Ser Val Gly Thr Leu Lys
        300                 305                 310
Glu Glu Val Gln Lys Leu Asp Asp Leu Tyr Gln Gln Lys Ile Lys Glu
    315                 320                 325
Ala Glu Glu Glu Asp Glu Lys Cys Ala Ser Glu Leu Glu Ser Leu Glu
330                 335                 340                 345
Lys His Lys His Leu Leu Glu Ser Thr Val Asn Gln Gly Leu Ser Glu
                350                 355                 360
Ala Met Asn Glu Leu Asp Ala Val Gln Arg Glu Tyr Gln Leu Val Val
            365                 370                 375
Gln Thr Thr Thr Glu Glu Arg Arg Lys Val Gly Asn Asn Leu Gln Arg
        380                 385                 390
Leu Leu Glu Met Val Ala Thr His Val Gly Ser Val Glu Lys His Leu
    395                 400                 405
Glu Glu Gln Ile Ala Lys Val Asp Arg Glu Tyr Glu Glu Cys Met Ser
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410 415 420 425

Glu Asp Leu Ser Glu Asn Ile Lys Glu Ile Arg Asp Lys Tyr Glu Lys

430 435 440

Lys Ala Thr Leu Ile Lys Ser Ser Glu Glu

445 450

<210> 41

<211> 1422

<212> DNA

<213> Homo sapiens

<400> 41

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atagactgca tcaagataca tactgccatg aaagaaagct caccttttatt tgatgatggg 120

cagccttggg gagaagaaac tgaagatgga attatgcata ataagttgtt tttggactac 180

accataaaat gctatgagag ttttatgagt ggtgccgaca gctttgatga gatgaatgca 240

gagctgcagt caaaactgaa ggatttattt aatgtggatg cttttaagct ggaatcatta 300

gaagcaaaaa acagagcatt gaatgaacag attgcaagat tggaacaaga aagagaaaaa 360

gaaccgaatc gtctagagtc gttgagaaaa ctgaaggctt ccttacaagg agatgttcaa 420

aagtatcagg catacatgag caatttggag tctcattcag ccattcttga ccagaaatta 480

aatggtctca atgaggaaat tgctagagta gaactagaat gtgaaacaat aaaacaggag 540

aacactcgac tacagaatat cattgacaac cagaagtact cagttgcaga cattgagcga 600

ataaatcatg aaagaaatga attgcagcag actattaata aattaaccaa ggacctggaa 660

gctgaacaac agaagttgtg gaatgaggag ttaaaatatg ccagaggcaa agaagcgatt 720

gaaacacaat tagcagagta tcacaaattg gctagaaaat taaaacttat tcctaaaggt 780

gctgagaatt ccaaaggtta tgactttgaa attaagttta atcccgaggc tggtgccaac 840

tgcctgtca aatacagggc tcaagtttat gtacctctta aggaactcct gaatgaaact 900

gaagaagaaa ttaataaagc cctaaataaa aaaatgggtt tggaggatac tttagaacaa 960

ttgaatgcaa tgataacaga aagcaagaga agtgtgggaa ctctgaaaga agaagttcaa 1020

aagctggatg atctttacca acaaaaaatt aaggaagcag aggaaggagg tgaaaaatgt 1080

gccagtgagc ttgagtcctt ggagaaacac aagcacctgc tagaaagtac tgttaaccag 1140

gggctcagtg aagctatgaa tgaattagat gctgttcagc gggaatacca actagttgtg 1200

caaaccacga ctgaagaaag acgaaaagtg ggaaataact tgcaacgtct gttagagatg 1260

gttgctacac atgttgggtc tgtagagaaa catcttgagg agcagattgc taaagttgat 1320

agaggatatg aaggatgcat gtcagaagat ctctcggaaa atattaaaga gattagagat 1380

aagtatgaga agaaagctac tctaattaag tcttctgaag aa 1422

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<400> 42
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                                          Met Tyr Thr Val Gly
                                          -23         -20
gct cct cat aca tgg cct cac att gtg gca gcc tta gtt tgg cta ata     161
Ala Pro His Thr Trp Pro His Ile Val Ala Ala Leu Val Trp Leu Ile
        -15                 -10                 -5
gac tgc atc aag ata cat act gcc atg aaa gaa agc tca cct tta ttt     209
Asp Cys Ile Lys Ile His Thr Ala Met Lys Glu Ser Ser Pro Leu Phe
        1               5                   10
gat gat ggg cag cct tgg gga gaa gaa act gaa gat gga att atg cat     257
Asp Asp Gly Gln Pro Trp Gly Glu Glu Thr Glu Asp Gly Ile Met His
15                  20                  25                  30
aat aag ttg ttt ttg gac tac acc ata aaa tgc tat gag agt ttc atg     305
Asn Lys Leu Phe Leu Asp Tyr Thr Ile Lys Cys Tyr Glu Ser Phe Met
                35                  40                  45
agt ggt gcc gac agc ttt gat gag atg aat gca gag ctg cag tca aaa     353
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Ser Gly Ala Asp Ser Phe Asp Glu Met Asn Ala Glu Leu Gln Ser Lys
                50                  55                  60
ctg aag gat tta ttt aat gtg gat gct ttt aag ctg gaa tca tta gaa   401
Leu Lys Asp Leu Phe Asn Val Asp Ala Phe Lys Leu Glu Ser Leu Glu
        65                  70                  75
gca aaa aac aga gca ttg aat gaa cag att gca aga ttg gaa caa gaa   449
Ala Lys Asn Arg Ala Leu Asn Glu Gln Ile Ala Arg Leu Glu Gln Glu
    80                  85                  90
aga gaa aaa gaa ccg aat cgt cta gag tcg ttg aga aaa ctg aag gct   497
Arg Glu Lys Glu Pro Asn Arg Leu Glu Ser Leu Arg Lys Leu Lys Ala
95                  100                 105                 110
TCC TTA CAA GGA GAT GTT CAA AAG TAT CAG GCA TAC ATG AGC AAT TTG   545
Ser Leu Gln Gly Asp Val Gln Lys Tyr Gln Ala Tyr Met Ser Asn Leu
                115                 120                 125
gag tct cat tca gcc att ctt gac cag aaa tta aat ggt ctc aat gag   593
Glu Ser His Ser Ala Ile Leu Asp Gln Lys Leu Asn Gly Leu Asn Glu
            130                 135                 140
gaa att gct aga gta gaa cta gaa tgt gaa aca ata aaa cag gag aac   641
Glu Ile Ala Arg Val Glu Leu Glu Cys Glu Thr Ile Lys Gln Glu Asn
        145                 150                 155
act cga cta cag aat atc att gac aac cag aag tac tca gtt gca gac   689
Thr Arg Leu Gln Asn Ile Ile Asp Asn Gln Lys Tyr Ser Val Ala Asp
    160                 165                 170
att gag cga ata aat cat gaa aga aat gaa ttg cag cag act att aat   737
Ile Glu Arg Ile Asn His Glu Arg Asn Glu Leu Gln Gln Thr Ile Asn
175                 180                 185                 190
aaa tta acc aag gac ctg gaa gct gaa caa cag aag ttg tgg aat gag   785
Lys Leu Thr Lys Asp Leu Glu Ala Glu Gln Gln Lys Leu Trp Asn Glu
                195                 200                 205
gag tta aaa tat gcc aga ggc aaa gaa gcg att gaa aca caa tta gca   833
Glu Leu Lys Tyr Ala Arg Gly Lys Glu Ala Ile Glu Thr Gln Leu Ala
            210                 215                 220
gag tat cac aaa ttg gct aga aaa tta aaa ctt att cct aaa ggt gct   881
Glu Tyr His Lys Leu Ala Arg Lys Leu Lys Leu Ile Pro Lys Gly Ala
        225                 230                 235
gag aat tcc aaa ggt tat gac ttt gat att aag ttt aat ccc gag gct   929
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Glu Asn Ser Lys Gly Tyr Asp Phe Glu Ile Lys Phe Asn Pro Glu Ala
  240                 245                 250
ggt gcc aac tgc ctt gtc aaa tac agg gct caa gtt tat gta cct ctt   977
Gly Ala Asn Cys Leu Val Lys Tyr Arg Ala Gln Val Tyr Val Pro Leu
255                 260                 265                 270
aag gaa ctc ctg aat gaa act gaa gaa gaa att aat aaa gcc cta aat  1025
Lys Glu Leu Leu Asn Glu Thr Glu Glu Glu Ile Asn Lys Ala Leu Asn
                275                 280                 285
aaa aaa atg ggt ttg gag gat act tta gaa caa ttg aat gca atg ata  1073
Lys Lys Met Gly Leu Glu Asp Thr Leu Glu Gln Leu Asn Ala Met Ile
            290                 295                 300
aca gaa agc aag aga agt gtg gga act ctg aaa gaa gaa gtt caa aag  1121
Thr Glu Ser Lys Arg Ser Val Gly Thr Leu Lys Glu Glu Val Gln Lys
        305                 310                 315
ctg gat gat ctt tac caa caa aaa att aag gaa gca gag gaa gag gat  1169
Leu Asp Asp Leu Tyr Gln Gln Lys Ile Lys Glu Ala Glu Glu Glu Asp
    320                 325                 330
gaa aaa tgt gcc agt gag ctt gag tcc ttg gag aaa cac aag cac ctg  1217
Glu Lys Cys Ala Ser Glu Leu Glu Ser Leu Glu Lys His Lys His Leu
335                 340                 345                 350
cta gaa agt act gtt aac cag ggg ctc agt gaa gct atg aat gaa tta  1265
Leu Glu Ser Thr Val Asn Gln Gly Leu Ser Glu Ala Met Asn Glu Leu
                355                 360                 365
gat gct gtt cag cgg gaa tac caa cta gtt gtg caa acc acg act gaa  1313
Asp Ala Val Gln Arg Glu Tyr Gln Leu Val Val Gln Thr Thr Thr Glu
            370                 375                 380
gaa aga cga aaa gtg gga aat aac ttg caa cgt ctg tta gag atg gtt  1361
Glu Arg Arg Lys Val Gly Asn Asn Leu Gln Arg Leu Leu Glu Met Val
        385                 390                 395
gct aca cat gtt ggg tct gta gag aaa cat ctt gag gag cag att gct  1409
Ala Thr His Val Gly Ser Val Glu Lys His Leu Glu Glu Gln Ile Ala
    400                 405                 410
aaa gtt gat aga gaa tat gaa gaa tgc atg tca gaa gat ctc tcg gaa  1457
Lys Val Asp Arg Glu Tyr Glu Glu Cys Met Ser Glu Asp Leu Ser Glu
415                 420                 425                 430
aat att aaa gag att agt gat aag tat gag aag aaa gct act cta att  1505
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Asn Ile Lys Glu Ile Arg Asp Lys Tyr Glu Lys Lys Ala Thr Leu Ile
435 440 445

aag tct tct gaa gaa tgaagataaa atgttgatca tgtatatata tccatagtga 1560
Lys Ser Ser Glu Glu
450

ataaaattgt ctcagtaaag taaaaaaaaa aaaaaaaaaa aaaaaaaaaa aaa 1613

<210> 43
<211> 78
<212> PRT
<213> Homo sapiens

<400> 43
Met Tyr Tyr Ile Leu Ile Tyr Pro Phe Pro Leu Phe Leu Phe Leu Leu
-22 -20 -15 -10
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-5 1 5 10
Phe Asp Leu Pro Lys His Leu Val Asn Leu Ile Phe Val Thr Leu Trp
15 20 25
Met Val Asn Leu Thr Phe Thr Gln Val Gly Phe Cys Phe Val Glu Asn
30 35 40
Asp Leu Leu Gly Gly Thr Thr Thr Thr Glu Arg Thr Lys Leu
45 50 55

<210> 44
<211> 234
<212> DNA
<213> Homo sapiens

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aatttaatct ttgtaacact ttggatggtt aacttaacct ttactcaagt tggtttttgt 180
tttgttgaaa atgacttact tggtggaacc actactactg aaagaacgaa actt 234

<210> 45

<211> 511
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<213> Homo sapiens

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                                                  -22  -20

att tta atc tat cct ttt cct ttg ttt ttg ttc tta tta tct ctt ctg    105
Ile Leu Ile Tyr Pro Phe Pro Leu Phe Leu Phe Leu Leu Ser Leu Leu
            -15                 -10                 -5

ata tat aac caa aaa atg aaa aaa tct gta cac ttg gtg ttt gat tta    153
Ile Tyr Asn Gln Lys Met Lys Lys Ser Val His Leu Val Phe Asp Leu
        1               5                   10

cct aag cac cta gtt aat tta atc ttt gta aca ctt tgg atg gtt aac    201
Pro Lys His Leu Val Asn Leu Ile Phe Val Thr Leu Trp Met Val Asn
    15                  20                  25

tta acc ttt act caa gtt ggt ttt tgt ttt gtt gaa aat gac tta ctt    249
Leu Thr Phe Thr Gln Val Gly Phe Cys Phe Val Glu Asn Asp Leu Leu
30                  35                  40                  45

ggt gga acc act act act gaa aga acg aaa ctt tgatattaca ttgttaagta  302
Gly Gly Thr Thr Thr Thr Glu Arg Thr Lys Leu
                50                  55

tcagagctgt tacagagcaa gtcctttaa agagatgtaa aaattaagta cctgtgccaa   362
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actgatttt attagaaacc ctgttttctt taagtaaaag tatattctac cagcatggct 422
tggtaagaaa aatcccctat ctttttttcc ctgtcctcaa aattcagaat ttttccggaa 482
aaaaaaaaaa aaaaaaaaaa aaaaaaaaa 511

<210> 46
<211> 73
<212> PRT
<213> Homo sapiens

<400> 46

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			5					10					15		
Leu	Cys	Asp	Gly	Gly	Leu	Ile	Val	Ser	Val	Phe	Thr	Gln	Gly	Trp	Phe
		20					25					30			
Pro	Gly	Cys	Thr	Ala	Pro	Val	Pro	Thr	Pro	Thr	Val	Pro	Leu	Ile	Arg
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<212> DNA
<213> Homo sapiens

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<210> 48
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<400> 48

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ggt ttt tcc tgc tcc tgg ggt aac aca tgc gct tgt cat aca cgc ccc    102
Gly Phe Ser Cys Ser Trp Gly Asn Thr Cys Ala Cys His Thr Arg Pro
        -5                  1               5

ttc ctt gcc cct tca gta ttc tct ctt tgc gat gga ggt ctc ata gtg    150
Phe Leu Ala Pro Ser Val Phe Ser Leu Cys Asp Gly Gly Leu Ile Val
 10                  15                  20                  25

agt gtc ttc act caa ggg tgg ttt cct ggc tgc acg gca cct gtt cca    198
Ser Val Phe Thr Gln Gly Trp Phe Pro Gly Cys Thr Ala Pro Val Pro
                30                  35                  40

aca cct act gtg cct ctc atc agg tgt cac gat ttt tct gcc act tca    246
Thr Pro Thr Val Pro Leu Ile Arg Cys His Asp Phe Ser Ala Thr Ser
            45                  50                  55

cct tagggagctt ccagtgattg attttaggag gcccacgcca agctccccag          299
Pro

gaaatgactg ccttccttgg gaccaaggac cgttccaacg gcattcactg ccagttctaa   359
tagccgagga aaatgcccga ggcgctgtct tctgtccccc acacgtacca gaaagtgaaa   419
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gtgattctag acttcagata tatttaggaa ggcgcagatt tcaaatctgt gtttgatttt 839
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<212> PRT
<213> Homo sapiens

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20 25 30
Leu Lys Leu Asn Phe Trp Lys Ser Pro Ser Ser Phe Asn Arg Pro Val
35 40 45
Asp Val Leu Val Pro Ser Val Ser Leu Gln Ala Phe Lys Ser Phe Leu
50 55 60
Arg Ser Gln Gly Leu Glu Tyr Ala Val Thr Ile Glu Asp Leu Gln Ala
65 70 75 80
Leu Leu Asp Asn Glu Asp Asp Glu Met Gln His Asn Glu Gly Gln Glu
85 90 95
Arg Ser Ser Asn Asn Phe Asn Tyr Gly Ala Tyr His Ser Leu Glu Ala
100 105 110
Thr Tyr His Glu Met Asp Asn Ile Ala Ala Asp Phe Pro Asp Leu Ala
115 120 125
Arg Arg Val Lys Ile Gly His Ser Phe Glu Asn Arg Thr Met Tyr Val
130 135 140
Leu Lys Phe Ser Thr Gly Lys Gly Val Arg Arg Pro Ala Val Trp Leu
145 150 155 160
Asn Ala Gly Ile His Ser Arg Glu Trp Ile Ser Gln Ala Thr Ala Ile

165 170 175

Trp Thr Ala Arg Lys Ile Val Ser Asp Tyr Gln Arg Asp Pro Ala Ile

180 185 190

Thr Ser Ile Leu Glu Lys Met Asp Ile Phe Leu Leu Pro Val Ala Asn

195 200 205

Pro Asp Gly Tyr Val Tyr Thr Gln Thr Gln Asn Arg Leu Trp Arg Lys

210 215 220

Thr Arg Ser Arg Asn Pro Gly Ser Ser Cys Ile Gly Ala Asp Pro Asn

225 230 235 240

Arg Asn Trp Asn Ala Ser Phe Ala Gly Lys Gly Ala Ser Asp Asn Pro

245 250 255

Cys Ser Glu Val Tyr His Gly Pro His Ala Asn Ser Glu Val Glu Val

260 265 270

Lys Ser Val Val Asp Phe Ile Gln Lys His Gly Asn Phe Lys Gly Phe

275 280 285

Ile Asp Leu His Ser Tyr Ser Gln Leu Leu Met Tyr Pro Tyr Gly Tyr

290 295 300

Ser Val Lys Lys Ala Pro Asp Ala Glu Glu Leu Asp Lys Val Ala Arg

305 310 315 320

Leu Ala Ala Lys Ala Leu Ala Ser Val Ser Gly Thr Glu Tyr Gln Val

325 330 335

Gly Pro Thr Cys Thr Thr Val Tyr Pro Ala Ser Gly Ser Ser Ile Asp

340 345 350

Trp Ala Tyr Asp Asn Gly Ile Lys Phe Ala Phe Thr Phe Glu Leu Arg

355 360 365

Asp Thr Gly Thr Tyr Gly Phe Leu Leu Pro Ala Asn Gln Ile Ile Pro

370 375 380

Thr Ala Glu Glu Thr Trp Leu Gly Leu Lys Thr Ile Met Glu His Val

385 390 395 400

Arg Asp Asn Leu Tyr

405

<210> 50

<211> 1263

<212> DNA

<213> Homo sapiens

<400> 50

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aatcggcctg tggatgtcct ggtcccatct gtcagtctgc aggcatttaa atccttcctg 240
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<400> 51

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agc atc tgt ggc caa gaa aaa ttt ttt ggg gac caa gtt ttt agg att      97
Ser Ile Cys Gly Gln Glu Lys Phe Phe Gly Asp Gln Val Phe Arg Ile
             1               5                  10

aat gtc aga aat gga gac gag atc agc aaa ttg agt caa cta gtg aat     145
Asn Val Arg Asn Gly Asp Glu Ile Ser Lys Leu Ser Gln Leu Val Asn
     15                  20                  25

tca aac aac ttg aag ctc aat ttc tgg aaa tct ccc tcc tcc ttc aat     193
Ser Asn Asn Leu Lys Leu Asn Phe Trp Lys Ser Pro Ser Ser Phe Asn
 30                  35                  40                  45

cgg cct gtg gat gtc ctg gtc cca tct gtc agt ctg cag gca ttt aaa     241
Arg Pro Val Asp Val Leu Val Pro Ser Val Ser Leu Gln Ala Phe Lys
                 50                  55                  60

tcc ttc ctg aga tcc cag ggc tta gag tac gca gtg acg att gag gac     289
Ser Phe Leu Arg Ser Gln Gly Leu Glu Tyr Ala Val Thr Ile Glu Asp
             65                  70                  75

ctg cag gcc ctt tta gac aat gaa gat gat gaa atg caa cac aat gaa     337
Leu Gln Ala Leu Leu Asp Asn Glu Asp Asp Glu Met Gln His Asn Glu
         80                  85                  90

ggg caa gaa cgg agc agt aat aac ttc aac tac ggg gct tac cat tcc     385
Gly Gln Glu Arg Ser Ser Asn Asn Phe Asn Tyr Gly Ala Tyr His Ser
     95                  100                 105

ctg gaa gct act tac cac gag atg gac aac att gcc gca gac ttt cct     433
Leu Glu Ala Thr Tyr His Glu Met Asp Asn Ile Ala Ala Asp Phe Pro
110                 115                 120                 125

gac ctg gcg agg agg gtg aag att gga cat tcg ttt gaa aac cgg acg     481
Asp Leu Ala Arg Arg Val Lys Ile Gly His Ser Phe Glu Asn Arg Thr
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Met Tyr Val Leu Lys Phe Ser Thr Gly Lys Gly Val Arg Arg Pro Ala
                145                 150                 155
gtt tgg ctg aat gca ggc atc cat tcc cga gag tgg atc tcc cag gcc   577
Val Trp Leu Asn Ala Gly Ile His Ser Arg Glu Trp Ile Ser Gln Ala
            160                 165                 170
act gca atc tgg acg gca agg aag att gta tct gat tac cag agg gat   625
Thr Ala Ile Trp Thr Ala Arg Lys Ile Val Ser Asp Tyr Gln Arg Asp
        175                 180                 185
cca gct atc acc tcc atc ttg gag aaa atg gat att ttc ttg ttg cct   673
Pro Ala Ile Thr Ser Ile Leu Glu Lys Met Asp Ile Phe Leu Leu Pro
    190                 195                 200                 205
gtg gcc aat cct gat gga tat gtg tat act caa act caa aac cga tta   721
Val Ala Asn Pro Asp Gly Tyr Val Tyr Thr Gln Thr Gln Asn Arg Leu
                210                 215                 220
tgg agg aag acg cgg tcc cga aat cct gga agc tcc tgc att ggt gct   769
Trp Arg Lys Thr Arg Ser Arg Asn Pro Gly Ser Ser Cys Ile Gly Ala
            225                 230                 235
gac cca aat aga aac tgg aac gct agt ttt gca gga aag gga gcc agc   817
Asp Pro Asn Arg Asn Trp Asn Ala Ser Phe Ala Gly Lys Gly Ala Ser
        240                 245                 250
gac aac cct tgc tcc gaa gtg tac cat gga ccc cac gcc aat tcg gaa   865
Asp Asn Pro Cys Ser Glu Val Tyr His Gly Pro His Ala Asn Ser Glu
    255                 260                 265
gtg gag gtg aaa tca gtg gta gat ttc atc caa aaa cat ggg aat ttc   913
Val Glu Val Lys Ser Val Val Asp Phe Ile Gln Lys His Gly Asn Phe
270                 275                 280                 285
aag ggc ttc atc gac ctg cac agc tac tcg cag ctg ctg atg tat cca   961
Lys Gly Phe Ile Asp Leu His Ser Tyr Ser Gln Leu Leu Met Tyr Pro
                290                 295                 300
tat ggg tac tca gtc aaa aag gcc cca gat gcc gag gaa ctc gac aag  1009
Tyr Gly Tyr Ser Val Lys Lys Ala Pro Asp Ala Glu Glu Leu Asp Lys
            305                 310                 315
gtg gcg agg ctt gcg gcc aaa gct ctg gct tct gtg tcg ggc act gag  1057
Val Ala Arg Leu Ala Ala Lys Ala Leu Ala Ser Val Ser Gly Thr Glu
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tac caa gtg ggt ccc acc tgc acc act gtc tat cca gct agc ggg agc   1105
Tyr Gln Val Gly Pro Thr Cys Thr Thr Val Tyr Pro Ala Ser Gly Ser
    335                 340                 345
agc atc gac tgg gcg tat gac aac ggc atc aaa ttt gca ttc aca ttt   1153
Ser Ile Asp Trp Ala Tyr Asp Asn Gly Ile Lys Phe Ala Phe Thr Phe
350                 355                 360                 365
gag ttg aga gat acc ggg acc tat ggc ttc ctc ctg cca gct aac cag   1201
Glu Leu Arg Asp Thr Gly Thr Tyr Gly Phe Leu Leu Pro Ala Asn Gln
                370                 375                 380
atc atc ccc act gca gag gag acg tgg ctg ggg ctg aag acc atc atg   1249
Ile Ile Pro Thr Ala Glu Glu Thr Trp Leu Gly Leu Lys Thr Ile Met
            385                 390                 395
gag cat gtg cgg gac aac ctc tac taggcgatgg ctctgctctg tctacattta  1303
Glu His Val Arg Asp Asn Leu Tyr
        400                 405
tttgtaccca cacgtgcacg cactgaggcc attgttaaag gagctctttc ctacctgtgt 1363
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<211> 111
<212> PRT
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<400> 52

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		5					10					15			
Lys	Gln	Gly	Glu	Tyr	Arg	Phe	Ser	Thr	Thr	Gln	Pro	Pro	Gln	Glu	Ser
	20					25					30				
Val	Asp	Arg	Trp	Gly	Lys	Cys	Cys	Leu	Pro	Trp	Ala	Leu	Gly	Cys	Arg
35					40					45					50
Lys	Lys	Thr	Pro	Lys	Ala	Lys	Tyr	Met	Tyr	Leu	Ala	Gln	Glu	Leu	Leu
				55					60					65	
Val	Asp	Pro	Glu	Trp	Pro	Pro	Lys	Pro	Gln	Thr	Thr	Thr	Glu	Ala	Lys
			70					75					80		
Ala	Leu	Val	Lys	Glu	Asn	Gly	Ser	Cys	Gln	Ile	Ile	Thr	Ile	Thr	
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<212> DNA
<213> Homo sapiens

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accacagcc caccgcagga gtcagtggat cggtgggga atgctgctt accctgggcc 180

ctgggctgta gaaagaagac accaaaggca aagtacatgt atctggcgca ggagctcttg 240
gttgatccag aatggccacc aaaacctcag acaaccacag aagctaaagc tttagttaag 300
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Val Asn Ala Phe Val Ser Ile Thr Val Glu Asn Phe Phe Leu Asp Met
-5 1 5

gtc ctt tgg aaa gtt gtg ttc aac cga gac aaa caa gga gag tat cgg 149
Val Leu Trp Lys Val Val Phe Asn Arg Asp Lys Gln Gly Glu Tyr Arg
10 15 20

ttc agc acc aca cag cca ccg cag gag tca gtg gat cgg tgg gga aaa 197
Phe Ser Thr Thr Gln Pro Pro Gln Glu Ser Val Asp Arg Trp Gly Lys
25 30 35 40

tgc tgc tta ccc tgg gcc ctg ggc tgt aga aag aag aca cca aag gca 245
Cys Cys Leu Pro Trp Ala Leu Gly Cys Arg Lys Lys Thr Pro Lys Ala

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                60                  65                  70
cca aaa cct cag aca acc aca gaa gct aaa gct tta gtt aag gag aat      341
Pro Lys Pro Gln Thr Thr Thr Glu Ala Lys Ala Leu Val Lys Glu Asn
        75                  80                  85
gga tca tgt caa atc atc acc ata aca tagcagtgaa tcagtctcag            388
Gly Ser Cys Gln Ile Ile Thr Ile Thr
    90                  95
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Leu Met Ile Met Leu Ser Arg Phe Glu Leu Tyr Gln Ile Phe Ser Thr
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Pro Asp Tyr Gly Lys Arg Phe Ser Ser Glu Ile Thr His Lys Asp Val
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Val Gln Gln Asn Asn Thr Leu Ile Glu Glu Met Leu Tyr Leu Ile Ile
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Thr Asp Glu Ile Lys Arg Glu Ile Ile His Gln Leu Ser Ile Lys Pro
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Met Ala His Ser Glu Leu Val Lys Ser Leu Pro Glu Asp Glu Asn Lys
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Glu Thr Gly Met Glu Ser Val Ile Glu Ala Val Ala His Phe Lys Lys
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Pro Gly Leu Thr Gly Arg Gly Met Tyr Glu Leu Lys Pro Glu Cys Ala
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Lys Glu Phe Asn Leu Tyr Phe Tyr His Phe Ser Arg Ala Glu Gln Ser
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Lys Ala Glu Glu Ala Gln Arg Lys Leu Lys Arg Gln Asn Arg Glu Asp
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Thr Ala Leu Pro Pro Pro Val Leu Pro Pro Phe Cys Pro Leu Phe Ala
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Ser Leu Val Asn Ile Leu Gln Ser Asp Val Met Leu Cys Ile Met Gly
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Thr Ile Leu Gln Trp Ala Val Glu His Asn Gly Tyr Ala Trp Ser Glu
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Ser Met Leu Gln Arg Val Leu His Leu Ile Gly Met Ala Leu Gln Glu
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Asp His Ser Pro Val Ala Ser Asp Met Thr Leu Thr Ala Leu Gly Pro
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Cys Gln Glu Glu Gln Glu Val Lys Val Glu Ser Arg Ala Met Val Leu
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Arg Gln Gln Arg Leu Arg Leu His Thr Ser Tyr Asp Val Glu Asn Gly
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1 5 10 15

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Tyr Tyr His Asn Val Lys Cys Arg Arg Glu Met Phe Asp Lys Asp Val
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Val Met Leu Gln Thr Gly Val Ser Met Met Asp Pro Asn His Phe Leu
35 40 45

atg atc atg ctc agc cgc ttt gaa ctt tat cag att ttc agt act cca 298
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gac tat gga aaa aga ttt agt tct gag att acc cat aag gat gtt gtt 346
Asp Tyr Gly Lys Arg Phe Ser Ser Glu Ile Thr His Lys Asp Val Val
65 70 75

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Gln Gln Asn Asn Thr Leu Ile Glu Glu Met Leu Tyr Leu Ile Ile Met
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Leu Val Gly Glu Arg Phe Ser Pro Gly Val Gly Gln Val Asn Ala Thr
100 105 110

gat gaa atc aag cga gag att atc cat cag ttg agt atc aag cct atg 490
Asp Glu Ile Lys Arg Glu Ile Ile His Gln Leu Ser Ile Lys Pro Met
115 120 125

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act ggc atg gag agt gta atc gaa gca gtt gcc cat ttc aag aaa cct      586
Thr Gly Met Glu Ser Val Ile Glu Ala Val Ala His Phe Lys Lys Pro
    145                 150                 155
gga tta aca gga cga ggc atg tat gaa ctg aaa cca gaa tgt gcc aaa      634
Gly Leu Thr Gly Arg Gly Met Tyr Glu Leu Lys Pro Glu Cys Ala Lys
160                 165                 170                 175
gag ttc aac ttg tat ttc tat cac ttt tca agg gca gaa cag tcc aag      682
Glu Phe Asn Leu Tyr Phe Tyr His Phe Ser Arg Ala Glu Gln Ser Lys
                180                 185                 190
gca gaa gaa gcg caa cgg aaa ttg aaa aga caa aat aga gaa gat aca      730
Ala Glu Glu Ala Gln Arg Lys Leu Lys Arg Gln Asn Arg Glu Asp Thr
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Ala Leu Pro Pro Pro Val Leu Pro Pro Phe Cys Pro Leu Phe Ala Ser
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Leu Val Asn Ile Leu Gln Ser Asp Val Met Leu Cys Ile Met Gly Thr
    225                 230                 235
att ctg caa tgg gct gtg gaa cat aat gga tat gcc tgg tca gag tcc      874
Ile Leu Gln Trp Ala Val Glu His Asn Gly Tyr Ala Trp Ser Glu Ser
240                 245                 250                 255
atg ctg caa agg gtg tta cat tta att ggc atg gca cta caa gaa gaa      922
Met Leu Gln Arg Val Leu His Leu Ile Gly Met Ala Leu Gln Glu Glu
                260                 265                 270
aaa caa cat tta gag aat gtc acg gaa gag cat gta gta aca ttt acc      970
Lys Gln His Leu Glu Asn Val Thr Glu Glu His Val Val Thr Phe Thr
            275                 280                 285
ttc act cag aag ata tca aaa cct ggt gaa gcg cca aaa aat tct cct     1018
Phe Thr Gln Lys Ile Ser Lys Pro Gly Glu Ala Pro Lys Asn Ser Pro
        290                 295                 300
agc ata cta gct atg ctg gaa aca cta caa aat gct ccc tac cta gaa     1066
Ser Ile Leu Ala Met Leu Glu Thr Leu Gln Asn Ala Pro Tyr Leu Glu
    305                 310                 315
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aaa aag atg agg gag agt tca cct acc agt ccc gtg gca gag aca gaa  1162
Lys Lys Met Arg Glu Ser Ser Pro Thr Ser Pro Val Ala Glu Thr Glu
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gga acc ata atg gaa gag agt tca agg gac aaa gac aaa gct gag agg  1210
Gly Thr Ile Met Glu Glu Ser Ser Arg Asp Lys Asp Lys Ala Glu Arg
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aag aga aaa gca gag att gcc aga ctg cgc aga gaa aag atc atg gct  1258
Lys Arg Lys Ala Glu Ile Ala Arg Leu Arg Arg Glu Lys Ile Met Ala
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cag atg tct gaa atg cag cgg cat ttt att gat gaa aac aaa gaa ctc  1306
Gln Met Ser Glu Met Gln Arg His Phe Ile Asp Glu Asn Lys Glu Leu
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cat agc cct gtg gct tca gat atg aca ctt aca gca ctg ggc ccc gca  1402
His Ser Pro Val Ala Ser Asp Met Thr Leu Thr Ala Leu Gly Pro Ala
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Gln Glu Glu Gln Glu Val Lys Val Glu Ser Arg Ala Met Val Leu Ala
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Ala Phe Val Gln Arg Ser Thr Val Leu Ser Lys Asn Arg Ser Lys Phe
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att caa gat cca gaa aaa tat gat cca tta ttc atg cac cct gat ctg  1594
Ile Gln Asp Pro Glu Lys Tyr Asp Pro Leu Phe Met His Pro Asp Leu
480                 485                 490                 495
tct tgt gga aca cac act agt agc tgt ggg cac att atg cat gcc cat  1642
Ser Cys Gly Thr His Thr Ser Ser Cys Gly His Ile Met His Ala His
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caa cag aga tta cgc tta cat acg agc tat gat gta gaa aac gga gaa   1738
Gln Gln Arg Leu Arg Leu His Thr Ser Tyr Asp Val Glu Asn Gly Glu
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ttc ctt tgc ccc ctt tgt gaa tgc ttg agt aat act gtt att cct ctg   1786
Phe Leu Cys Pro Leu Cys Glu Cys Leu Ser Asn Thr Val Ile Pro Leu
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ctg ctt tct cca aga aat att ttt aac aac agg tta aat ttt tca gac   1834
Leu Leu Ser Pro Arg Asn Ile Phe Asn Asn Arg Leu Asn Phe Ser Asp
560                 565                 570                 575

caa cca aat ctg act cag tgg att aga aca ata tct cag caa ata aaa   1882
Gln Pro Asn Leu Thr Gln Trp Ile Arg Thr Ile Ser Gln Gln Ile Lys
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gca tta cag ttt ctt agg aaa gaa gaa agt act cct aat aat gcc tct   1930
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aca aag aat tca gaa aat gtg gat gaa tta cag ctc cct gaa ggg ttc   1978
Thr Lys Asn Ser Glu Asn Val Asp Glu Leu Gln Leu Pro Glu Gly Phe
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agg cct gat ttt cgt cct aag atc cct tat tct gag agc ata aaa gaa   2026
Arg Pro Asp Phe Arg Pro Lys Ile Pro Tyr Ser Glu Ser Ile Lys Glu
    625                 630                 635

atg cta acg aca ttt gga act gct acc tac aag gtg gga cta aag gtt   2074
Met Leu Thr Thr Phe Gly Thr Ala Thr Tyr Lys Val Gly Leu Lys Val
640                 645                 650                 655

cat ccc aat gaa gag gat cct cgt gtt ccc ata atg tgt tgg ggt agc   2122
His Pro Asn Glu Glu Asp Pro Arg Val Pro Ile Met Cys Trp Gly Ser
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tgc gcg tac acc atc caa agc ata gaa aga att ttg agt gat gaa gat   2170
Cys Ala Tyr Thr Ile Gln Ser Ile Glu Arg Ile Leu Ser Asp Glu Asp
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aaa cca ttg ttt ggt cct tta cct tgc aga ctg gat gac tgt ctt agg   2218
Lys Pro Leu Phe Gly Pro Leu Pro Cys Arg Leu Asp Asp Cys Leu Arg
        690                 695                 700
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    705                 710                 715

gtg gtg caa gga cat ttt tgt aaa ctt ttt gca tca ctg gtg cct aat  2314
Val Val Gln Gly His Phe Cys Lys Leu Phe Ala Ser Leu Val Pro Asn
720                 725                 730                 735

gac agc cat gag gaa ctt cca tgc ata tta gat att gac atg ttt cat  2362
Asp Ser His Glu Glu Leu Pro Cys Ile Leu Asp Ile Asp Met Phe His
                740                 745                 750

tta ttg gtg ggc ttg gtg ctt gca ttt cct gcg ttg cag tgt cag gat  2410
Leu Leu Val Gly Leu Val Leu Ala Phe Pro Ala Leu Gln Cys Gln Asp
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ttt tca ggg atc agc ctt ggc act gga gac ctt cac att ttc cat ctg  2458
Phe Ser Gly Ile Ser Leu Gly Thr Gly Asp Leu His Ile Phe His Leu
        770                 775                 780

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Val Thr Met Ala His Ile Ile Gln Ile Leu Leu Thr Ser Cys Thr Glu
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gag aat ggc atg gat caa gaa aat ccc cct tgt gaa gaa gaa tca gca  2554
Glu Asn Gly Met Asp Gln Glu Asn Pro Pro Cys Glu Glu Glu Ser Ala
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gtt ctt gct ttg tat aaa aca ctt cac cag tat acg gga agt gcc ttg  2602
Val Leu Ala Leu Tyr Lys Thr Leu His Gln Tyr Thr Gly Ser Ala Leu
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aaa gaa ata cca tcc ggc tgg cat ctg tgg agg agt gtc aga gct gga  2650
Lys Glu Ile Pro Ser Gly Trp His Leu Trp Arg Ser Val Arg Ala Gly
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atc atg cct ttc ctg aag tgt tct gct tta ttt ttt cat tac tta aat  2698
Ile Met Pro Phe Leu Lys Cys Ser Ala Leu Phe Phe His Tyr Leu Asn
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Gly Val Pro Ser Pro Pro Asp Ile Gln Val Pro Gly Thr Ser His Phe
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gaa cat tta tgt agc tat ctt tcc cta cca aac aac ctc att tgc ctt  2794
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cgt aac agt gaa gtt aaa aga tat cta gaa ggt gaa aga gat gct ata  2890
Arg Asn Ser Glu Val Lys Arg Tyr Leu Glu Gly Glu Arg Asp Ala Ile
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aga tat cca aga gaa tct aac aaa tta ata aac ctt cca gag gat tac  2938
Arg Tyr Pro Arg Glu Ser Asn Lys Leu Ile Asn Leu Pro Glu Asp Tyr
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ctg tgc tcc cag agt tac tgc tgc cag act gaa ctg gaa ggg gag gat  3082
Leu Cys Ser Gln Ser Tyr Cys Cys Gln Thr Glu Leu Glu Gly Glu Asp
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gta gga gcc tgc aca gct cac acc tac tcc tgt ggc tct gga gtg ggc  3130
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acc aaa ggc tgt ttt tat tct cct cct tac ctt gat gac tat ggg gag  3226
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gaa att gga cat gca cag gaa gcc aat cag acg ctg gtt ggc att gac  3370
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Tyr Cys Gln His Leu Ala Ser Ile Ser His Phe Met Gln Phe Pro His
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gag cta tca gaa act atc ctc acc atg gta gcc aat tgc agt aat gtt     97
Glu Leu Ser Glu Thr Ile Leu Thr Met Val Ala Asn Cys Ser Asn Val
             5                  10                  15

atg aat aag gcc aga caa cca cca cct gga gtt atg cca aaa gga cgt    145
Met Asn Lys Ala Arg Gln Pro Pro Pro Gly Val Met Pro Lys Gly Arg
        20                  25                  30

cct cct agt gct agc agc tta gat gcc att tct cct gtt cag att gac    193
Pro Pro Ser Ala Ser Ser Leu Asp Ala Ile Ser Pro Val Gln Ile Asp
    35                  40                  45

cct ctt gct gga atg aca tct ctt agt ata ggt ggt tca gct gcc cct    241
Pro Leu Ala Gly Met Thr Ser Leu Ser Ile Gly Gly Ser Ala Ala Pro
50                  55                  60                  65

cac acc cag agt atg cag ggt ttt cct cca aat ttg ggt tct gca ttc    289
His Thr Gln Ser Met Gln Gly Phe Pro Pro Asn Leu Gly Ser Ala Phe
                70                  75                  80

agt acc cct cag tca cca gca aat gca ttt cca ccc ctt tca acc ccc    337
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Ser Thr Pro Gln Ser Pro Ala Lys Ala Phe Pro Pro Leu Ser Thr Pro
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aat cag acc act gca ttc agt ggt att gga gga ctt tca tca cag ctt   385
Asn Gln Thr Thr Ala Phe Ser Gly Ile Gly Gly Leu Ser Ser Gln Leu
        100                 105                 110
cca gta ggt ggt ctt ggc aca ggc agc ctg act ggt ata gga act ggt   433
Pro Val Gly Gly Leu Gly Thr Gly Ser Leu Thr Gly Ile Gly Thr Gly
    115                 120                 125
gct ctt gga ctc cct gca gtg aat aac gac cct ttt gta cag agg aaa   481
Ala Leu Gly Leu Pro Ala Val Asn Asn Asp Pro Phe Val Gln Arg Lys
130                 135                 140                 145
ctg ggc acc tct gga ctg aat cag cct aca ttc cag cag agt aag atg   529
Leu Gly Thr Ser Gly Leu Asn Gln Pro Thr Phe Gln Gln Ser Lys Met
                150                 155                 160
aaa cct tcg gac ttg tct cag gtg tgg cca gag gca aac cag cac ttt   577
Lys Pro Ser Asp Leu Ser Gln Val Trp Pro Glu Ala Asn Gln His Phe
            165                 170                 175
agt aaa gag ata gat gat gaa gca aac agc tat ttc cag cga ata tat   625
Ser Lys Glu Ile Asp Asp Glu Ala Asn Ser Tyr Phe Gln Arg Ile Tyr
        180                 185                 190
aat cat cca cca cat cca acc atg tct gtt gat gag gta tta gaa atg   673
Asn His Pro Pro His Pro Thr Met Ser Val Asp Glu Val Leu Glu Met
    195                 200                 205
ctg cag aga ttt aaa gac tct act ata aag agg gaa cga gaa gta ttt   721
Leu Gln Arg Phe Lys Asp Ser Thr Ile Lys Arg Glu Arg Glu Val Phe
210                 215                 220                 225
aac tgt atg cta agg aac ttg ttt gaa gaa tat cgt ttt ttt ccc cag   769
Asn Cys Met Leu Arg Asn Leu Phe Glu Glu Tyr Arg Phe Phe Pro Gln
                230                 235                 240
tat cct gat aaa gag tta cat ata aca gcc tgc cta ttt ggt ggt ata   817
Tyr Pro Asp Lys Glu Leu His Ile Thr Ala Cys Leu Phe Gly Gly Ile
            245                 250                 255
att gag aaa gga ctg gtc act tac atg gca cta ggt ctg gct cta cga   865
Ile Glu Lys Gly Leu Val Thr Tyr Met Ala Leu Gly Leu Ala Leu Arg
        260                 265                 270
tat gtt ctt gaa gcc tta cgc aag cct ttt gga tcc aaa atg tat tat   913
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Tyr Val Leu Glu Ala Leu Arg Lys Pro Phe Gly Ser Lys Met Tyr Tyr
    275                 280                 285

ttc ggg att gct gca cta gat aga ttt aaa aac aga ttg aag gac tat    961
Phe Gly Ile Ala Ala Leu Asp Arg Phe Lys Asn Arg Leu Lys Asp Tyr
290                 295                 300                 305

ccc cag tat tgt caa cat ttg gct tct atc agt cac ttt atg caa ttt   1009
Pro Gln Tyr Cys Gln His Leu Ala Ser Ile Ser His Phe Met Gln Phe
                310                 315                 320

cca cat cat tta cag gag tat att gag tat gga cag cag tct aga gat   1057
Pro His His Leu Gln Glu Tyr Ile Glu Tyr Gly Gln Gln Ser Arg Asp
            325                 330                 335

cct cct gtg aaa atg caa ggc tct atc aca acc cct gga agt att gca   1105
Pro Pro Val Lys Met Gln Gly Ser Ile Thr Thr Pro Gly Ser Ile Ala
        340                 345                 350

ctg gct cag gcc cag gct cag gcc cag gtt cca gca aaa gct cct ctt   1153
Leu Ala Gln Ala Gln Ala Gln Ala Gln Val Pro Ala Lys Ala Pro Leu
    355                 360                 365

gct ggt caa gtt agc act atg gta acc acc tca aca act acc act gtt   1201
Ala Gly Gln Val Ser Thr Met Val Thr Thr Ser Thr Thr Thr Thr Val
370                 375                 380                 385

gct aaa acg gtt acg gtc acc agg cca act gga gtc agc ttt aag aaa   1249
Ala Lys Thr Val Thr Val Thr Arg Pro Thr Gly Val Ser Phe Lys Lys
                390                 395                 400

gat gtg cca cct tct att aat act aca aat ata gat acg ttg ctt gtg   1297
Asp Val Pro Pro Ser Ile Asn Thr Thr Asn Ile Asp Thr Leu Leu Val
            405                 410                 415

gcc aca gat caa act gag aga att gtg gag ccc cca gaa aat atc cag   1345
Ala Thr Asp Gln Thr Glu Arg Ile Val Glu Pro Pro Glu Asn Ile Gln
        420                 425                 430

gag aaa att gct ttt att ttc aat aat ctc tca cag tca aat atg aca   1393
Glu Lys Ile Ala Phe Ile Phe Asn Asn Leu Ser Gln Ser Asn Met Thr
    435                 440                 445

caa aag gtt gaa gag cta aag gaa acg gtg aaa gaa gaa ttt atg cct   1441
Gln Lys Val Glu Glu Leu Lys Glu Thr Val Lys Glu Glu Phe Met Pro
450                 455                 460                 465

tgg gtt tca cag tat ctg gtt atg aag aga gtc agt att gag cca aac   1489
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Trp Val Ser Gln Tyr Leu Val Met Lys Arg Val Ser Ile Glu Pro Asn
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ttt cat agc ctg tat tca aac ttc ctt gac acg ctg aag aat cct gaa  1537
Phe His Ser Leu Tyr Ser Asn Phe Leu Asp Thr Leu Lys Asn Pro Glu
            485                 490                 495

ttt aac aag atg gtt ctg aat gag acc tac aga aac att aaa gtg ctc  1585
Phe Asn Lys Met Val Leu Asn Glu Thr Tyr Arg Asn Ile Lys Val Leu
        500                 505                 510

ctg acc tct gat aaa gct gca gcc aat ttc tca gat cgt tct ttg ctg  1633
Leu Thr Ser Asp Lys Ala Ala Ala Asn Phe Ser Asp Arg Ser Leu Leu
    515                 520                 525

aag aac ttg gga cat tgg cta gga atg atc aca tta gct aaa aac aaa  1681
Lys Asn Leu Gly His Trp Leu Gly Met Ile Thr Leu Ala Lys Asn Lys
530                 535                 540                 545

ccc atc tta cac act gac ttg gat gtg aaa tca ttg ctg cta gag gct  1729
Pro Ile Leu His Thr Asp Leu Asp Val Lys Ser Leu Leu Leu Glu Ala
                550                 555                 560

tat gtt aaa gga caa caa gaa ttg ctc tat gta gtg ccc ttt gtt gcc  1777
Tyr Val Lys Gly Gln Gln Glu Leu Leu Tyr Val Val Pro Phe Val Ala
            565                 570                 575

aaa gtc tta gaa tct agc att cgt agt gtg gtt ttt agg cca cca aac  1825
Lys Val Leu Glu Ser Ser Ile Arg Ser Val Val Phe Arg Pro Pro Asn
        580                 585                 590

cct tgg aca atg gca att atg aat gta tta gct gag cta cat cag gag  1873
Pro Trp Thr Met Ala Ile Met Asn Val Leu Ala Glu Leu His Gln Glu
    595                 600                 605

cat gac tta aag tta aac ttg ang ttt gaa atc gag gtt ctc tgc aag  1921
His Asp Leu Lys Leu Asn Leu Lys Phe Glu Ile Glu Val Leu Cys Lys
610                 615                 620                 625

aac ctt gca tta gac atc aat gag cta aaa cct gga aac ctc cta aag  1969
Asn Leu Ala Leu Asp Ile Asn Glu Leu Lys Pro Gly Asn Leu Leu Lys
                630                 635                 640

gat aaa gat cgc ctg aag aat tta gat gag caa ctc tct gct cca aag  2017
Asp Lys Asp Arg Leu Lys Asn Leu Asp Glu Gln Leu Ser Ala Pro Lys
            645                 650                 655
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aaa gat gtc aag cag cca gaa gaa ctc cct ccc atc aca acc aca aca  2065
Lys Asp Val Lys Gln Pro Glu Glu Leu Pro Pro Ile Thr Thr Thr Thr
        660                 665                 670

act tct act aca cca gct acc aac acc act tgt aca gcc acg gtt cca  2113
Thr Ser Thr Thr Pro Ala Thr Asn Thr Thr Cys Thr Ala Thr Val Pro
    675                 680                 685

cca cag cca cag tac agc tac cac gac atc aat gtc tat tcc ctt gcg  2161
Pro Gln Pro Gln Tyr Ser Tyr His Asp Ile Asn Val Tyr Ser Leu Ala
690                 695                 700                 705

ggc ttg gca cca cac att act ctg aat cca aca att ccc ttg ttt cag  2209
Gly Leu Ala Pro His Ile Thr Leu Asn Pro Thr Ile Pro Leu Phe Gln
                710                 715                 720

gcc cat cca cag ttg aag cag tgt gtg cgt cag gca att gaa cgg gct  2257
Ala His Pro Gln Leu Lys Gln Cys Val Arg Gln Ala Ile Glu Arg Ala
            725                 730                 735

gtc cag gag ctg gtc cat cct gtg gtg gat cga tca att aag att gcc  2305
Val Gln Glu Leu Val His Pro Val Val Asp Arg Ser Ile Lys Ile Ala
        740                 745                 750

atg act act tgt gag caa ata gtc agg aag gat ttt gcc ctg gat tcg  2353
Met Thr Thr Cys Glu Gln Ile Val Arg Lys Asp Phe Ala Leu Asp Ser
    755                 760                 765

gag gaa tct cga atg cga ata gca gct cat cac atg atg cgt aac ttg  2401
Glu Glu Ser Arg Met Arg Ile Ala Ala His His Met Met Arg Asn Leu
770                 775                 780                 785

aca gct gga atg gct atg att aca tgc agg gaa cct ttg ctc atg agc  2449
Thr Ala Gly Met Ala Met Ile Thr Cys Arg Glu Pro Leu Leu Met Ser
                790                 795                 800

ata tct acc aac tta aaa aac agt ttt gcc tca gcc ctt cgt act gct  2497
Ile Ser Thr Asn Leu Lys Asn Ser Phe Ala Ser Ala Leu Arg Thr Ala
            805                 810                 815

tcc cca caa caa aga gaa atg atg gat cag gca gct gct caa tta gct  2545
Ser Pro Gln Gln Arg Glu Met Met Asp Gln Ala Ala Ala Gln Leu Ala
        820                 825                 830

cag gac aat tgt gag ttg gct tgc tgt ttt att cag aag act gca gtt  2593
Gln Asp Asn Cys Glu Leu Ala Cys Cys Phe Ile Gln Lys Thr Ala Val
    835                 840                 845
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gaa aaa gca ggc cct gag atg gac aag aga tta gca act gaa ttt gag  2641
Glu Lys Ala Gly Pro Glu Met Asp Lys Arg Leu Ala Thr Glu Phe Glu
850                 855                 860                 865
ctg aga aaa cat gct agg caa gaa gga cgc aga tac tgt gat cct gtt  2689
Leu Arg Lys His Ala Arg Gln Glu Gly Arg Arg Tyr Cys Asp Pro Val
                870                 875                 880
gtt tta aca tat caa gct gaa cgg atg cca gag caa atc agg ctg aaa  2737
Val Leu Thr Tyr Gln Ala Glu Arg Met Pro Glu Gln Ile Arg Leu Lys
            885                 890                 895
gtt ggt ggt gtg gac cca aag cag ttg gct gtt tat gaa gag ttt gca  2785
Val Gly Gly Val Asp Pro Lys Gln Leu Ala Val Tyr Glu Glu Phe Ala
        900                 905                 910
cgc aat gtt cct ggc ttc tta cct aca aat gac tta agt cag ccc acg  2833
Arg Asn Val Pro Gly Phe Leu Pro Thr Asn Asp Leu Ser Gln Pro Thr
    915                 920                 925
gga ttt tta gcc cag ccc atg aag caa gct tgg gca aca gat gat gta  2881
Gly Phe Leu Ala Gln Pro Met Lys Gln Ala Trp Ala Thr Asp Asp Val
930                 935                 940                 945
gct cag att tat gat aag tgt att aca gaa ctg gag caa cat cta cat  2929
Ala Gln Ile Tyr Asp Lys Cys Ile Thr Glu Leu Glu Gln His Leu His
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gcc atc cca cca act ttg gcc atg aac cct caa gct cag gct ctt cga  2977
Ala Ile Pro Pro Thr Leu Ala Met Asn Pro Gln Ala Gln Ala Leu Arg
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agt ctc ttg gag gtt gta gtt tta tct cga aac tct cgg gat gcc ata  3025
Ser Leu Leu Glu Val Val Val Leu Ser Arg Asn Ser Arg Asp Ala Ile
        980                 985                 990
gct gct ctt gga ttg ctc caa aag gct gta gag ggc tta cta gat gcc  3073
Ala Ala Leu Gly Leu Leu Gln Lys Ala Val Glu Gly Leu Leu Asp Ala
    995                 1000                1005
acn agt ggt gct gat gct gac ctt ctg ctg cgc tac agg gaa tgc cac  3121
Thr Ser Gly Ala Asp Ala Asp Leu Leu Leu Arg Tyr Arg Glu Cys His
1010                1015                1020                1025
ctc ttg gtc cta aaa gct ctg cag gat ggc cgg gca tat ggg tct ccn  3169
Leu Leu Val Leu Lys Ala Leu Gln Asp Gly Arg Ala Tyr Gly Ser Pro
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Trp Cys Asn Lys Gln Ile Thr Arg Cys Leu Ile Glu Cys Arg Asp Glu
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tat aaa tat aat gtg gag gct gtg gag ctg cta att cgc aat cat ttg  3265
Tyr Lys Tyr Asn Val Glu Ala Val Glu Leu Leu Ile Arg Asn His Leu
        1060                1065                1070

gtt aat atg cag cag tat gat ttt cac cta gcg cag tca atg gag aat  3313
Val Asn Met Gln Gln Tyr Asp Phe His Leu Ala Gln Ser Met Glu Asn
    1075                1080                1085

ggc tta aac tac atg gct gtg gca ttt gct atg cag tta gta aaa atc  3361
Gly Leu Asn Tyr Met Ala Val Ala Phe Ala Met Gln Leu Val Lys Ile
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ctg ctg gtg gat gaa agg agt gtt gct cat gtt act gag gca gat ctg  3409
Leu Leu Val Asp Glu Arg Ser Val Ala His Val Thr Glu Ala Asp Leu
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ttc cac acc att gaa acc ctc atg agg att aat gct cat tcc aga ggc  3457
Phe His Thr Ile Glu Thr Leu Met Arg Ile Asn Ala His Ser Arg Gly
            1125                1130                1135

aat gct cca gaa gga ttg tcc cag ctg atg gaa gta gtg cga tcc aac  3505
Asn Ala Pro Glu Gly Leu Ser Gln Leu Met Glu Val Val Arg Ser Asn
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tat gaa gca atg att gat cgt gct cat gga ggc cca aac ttt atg atg  3553
Tyr Glu Ala Met Ile Asp Arg Ala His Gly Gly Pro Asn Phe Met Met
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cat tct ggg atc tct caa gcc tca gag tat gat gac cct cca ggc ctg  3601
His Ser Gly Ile Ser Gln Ala Ser Glu Tyr Asp Asp Pro Pro Gly Leu
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agg gag aag gca gag tat ctt ctg agg gaa tgg gtg aat ctc tac cat  3649
Arg Glu Lys Ala Glu Tyr Leu Leu Arg Glu Trp Val Asn Leu Tyr His
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tca gca gca gct ggc cgc gac agt acc aaa gct ttc tct gca ttt gtt  3697
Ser Ala Ala Ala Gly Arg Asp Ser Thr Lys Ala Phe Ser Ala Phe Val
            1205                1210                1215

ggg cag atg cac cag caa ggg atc ctg aag acc gat gat ctc ata aca  3745
Gly Gln Met His Gln Gln Gly Ile Leu Lys Thr Asp Asp Leu Ile Thr
        1220                1225                1230
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agg ttc ttt cgt ctg tgt act gaa atg tgt gtt gaa atc agt tac cgt 3793
Arg Phe Phe Arg Leu Cys Thr Glu Met Cys Val Glu Ile Ser Tyr Arg
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gct cag gct gag cag cag cac aat cct gct gcc aat ccc acc atg atc 3841
Ala Gln Ala Glu Gln Gln His Asn Pro Ala Ala Asn Pro Thr Met Ile
1250 1255 1260 1265

cga gcc aag tgc tat cac aac ctg gat gcc ttt gtt cga ctc att gca 3889
Arg Ala Lys Cys Tyr His Asn Leu Asp Ala Phe Val Arg Leu Ile Ala
1270 1275 1280

ctg ctc gtg aaa cac tca ggg gag gcc acc aac act gtc aca aag att 3937
Leu Leu Val Lys His Ser Gly Glu Ala Thr Asn Thr Val Thr Lys Ile
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aat ctg ctg aac aag gtc ctt ggt ata gta gtg gga gtt ctc ctt cag 3985
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gat cat gat gtt cgt cag agt gaa ttt cag caa ctt ccc tac cat cga 4033
Asp His Asp Val Arg Gln Ser Glu Phe Gln Gln Leu Pro Tyr His Arg
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Ile Phe Ile Met Leu Leu Leu Glu Leu Asn Ala Pro Glu His Val Leu
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Leu Ile Ser His Arg Ile Phe Ile Ala Arg Met Leu Ala His Thr Pro
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Gln Gln Lys Gly Trp Pro Met Tyr Ala Gln Leu Leu Ile Asp Leu Phe
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Lys Tyr Leu Ala Pro Phe Leu Arg Asn Val Glu Leu Thr Lys Pro Met
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Asp Phe Pro Glu Phe Leu Cys Asp Tyr His Tyr Gly Phe Cys Asp Val
1445 1450 1455

atc cca cct aat tgt atc cag tta aga aat ttg atc ctg agt gcc ttt 4465
Ile Pro Pro Asn Cys Ile Gln Leu Arg Asn Leu Ile Leu Ser Ala Phe
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cca aga aac atg agg ctc ccc gac cca ttc act cct aat cta aag gtg 4513
Pro Arg Asn Met Arg Leu Pro Asp Pro Phe Thr Pro Asn Leu Lys Val
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Thr Gly Val Met Pro Pro Gln Phe Lys Lys Asp Leu Asp Ser Tyr Leu
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Lys Gly Ser Thr Pro Ser Met Ser Thr Ile Thr His Ser Ala His Met
1570 1575 1580 1585

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Leu Phe Leu Asn Ala Ile Ala Asn Gln Leu Arg Tyr Pro Asn Ser His
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Val Phe Ile Thr Lys Thr Phe Pro Asn His Tyr Ser Ile Val Thr Gly
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Asp Thr Ile Ser Ser Tyr Phe Met Asn Tyr Asn Ser Ser Val Ser Phe
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Glu Glu Arg Leu Asn Asn Ile Thr Met Trp Leu Asn Asn Ser Asn Pro
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Pro Val Thr Phe Ala Thr Leu Tyr Trp Glu Glu Pro Asp Ala Ser Gly
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His Lys Tyr Gly Pro Glu Asp Lys Glu Asn Met Ser Arg Val Leu Lys
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Lys Ile Asp Asp Leu Ile Gly Asp Leu Val Gln Arg Leu Lys Met Leu
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Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp His Gly Met
210 215 220 225
Thr Gln Cys Ser Gln Asp Arg Leu Ile Asn Leu Asp Ser Cys Ile Asp
230 235 240
His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala Ala Ile Leu
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Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Asn Arg Phe Tyr
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Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val Ala Asp Glu
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Gly Trp Thr Ile Val Leu Asn Glu Ser Ser Gln Lys Leu Gly Asp His
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Asp Ile Tyr Pro Met Met Cys His Ile Leu Gly Leu Lys Pro His Pro
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Cys Ile Asn Leu Pro Glu Ala Ile Ala Ile Val Ile Gly Ser Leu Leu
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Val Leu Thr Met Leu Thr Cys Leu Ile Ile Ile Met Gln Asn Arg Leu
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Asp Pro Leu Ile Gly
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<213> Homo sapiens

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catgttaaaa atgtttttat cacaaaaaca tttccaaacc actacagtat tgtgacaggc 240
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cactttctg actctaatga caaggatcct ttttggtgga atgaggcagt acctatttgg 360
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gaggaaagac taaataatat tactatgtgg ctaaacnatt cgaacccacc agtcaccttt 540
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tgcattaatc tcccagaagc catcgcgatt gttatcggtt cactcttggt gttaaccatg 1260
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gtgttcatt atg aag tta tta gta ata ctt ttg ttt tct gga ctt ata 108
Met Lys Leu Leu Val Ile Leu Leu Phe Ser Gly Leu Ile
-15 -10 -5
act ggt ttt aga agt gac tct tcc tct agt ttg cca cct aag tta cta 156
Thr Gly Phe Arg Ser Asp Ser Ser Ser Ser Leu Pro Pro Lys Leu Leu
1 5 10

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cta gta tcc ttt gat ggc ttc aga gct gat tat ctg aag aac tat gaa   204
Leu Val Ser Phe Asp Gly Phe Arg Ala Asp Tyr Leu Lys Asn Tyr Glu
 15                  20                  25                  30
ttt cct cat ctc cag aat ttt atc aaa gaa ggt gtt ttg gta gag cat   252
Phe Pro His Leu Gln Asn Phe Ile Lys Glu Gly Val Leu Val Glu His
                 35                  40                  45
GTT AAA AAT GTT TTT ATC ACA AAA ACA TTT CCA AAC CAC TAC AGT ATT   300
Val Lys Asn Val Phe Ile Thr Lys Thr Phe Pro Asn His Tyr Ser Ile
             50                  55                  60
gtg aca ggc ttg tat gaa gaa agc cat ggc att gtg gct aat tcc atg   348
Val Thr Gly Leu Tyr Glu Glu Ser His Gly Ile Val Ala Asn Ser MeT
         65                  70                  75
tat gat gca gtc aca aag aaa cac ttt tct gac tct aat gac aag gat   396
Tyr Asp Ala Val Thr Lys Lys His Phe Ser Asp Ser Asn Asp Lys Asp
     80                  85                  90
cct ttt tgg tgg aat gag gca gta cct att tgg gtg acc aat cag ctt   444
Pro Phe Trp Trp Asn Glu Ala Val Pro Ile Trp Val Thr Asn Gln Leu
 95                  100                 105                 110
cag gaa aac aga tca agt gct gct gct atg tgg cct ggt act gat gta   492
Gln Glu Asn Arg Ser Ser Ala Ala Ala Met Trp Pro Gly Thr Asp Val
                115                 120                 125
ccc att cac gat acc atc tct tcc tat ttt atg aat tac aac tcc tca   540
Pro Ile His Asp Thr Ile Ser Ser Tyr Phe Met Asn Tyr Asn Ser Ser
            130                 135                 140
gtg tca ttt gag gaa aga cta aat aat att act atg tgg cta aac aat   588
Val Ser Phe Glu Glu Arg Leu Asn Asn Ile Thr Met Trp Leu Asn Asn
        145                 150                 155
tcg aac cca cca gtc acc ttt gca aca cta tat tgg gaa gaa cca gat   636
Ser Asn Pro Pro Val Thr Phe Ala Thr Leu Tyr Trp Glu Glu Pro Asp
    160                 165                 170
gca agt ggc cac aaa tac gga cct gaa gat aaa gaa aac atg agc aga   684
Ala Ser Gly His Lys Tyr Gly Pro Glu Asp Lys Glu Asn Met Ser Arg
175                 180                 185                 190
gtg ttg aaa aaa atc gat gat ctt atc ggt gac tta gtc caa agt ctc   732
Val Leu Lys Lys Ile Asp Asp Leu Ile Gly Asp Leu Val Gln Arg Leu
                195                 200                 205
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aag atg tta ggg cta tgg gaa aat ctt aat gtg atc att aca agt gat   780
Lys Met Leu Gly Leu Trp Glu Asn Leu Asn Val Ile Ile Thr Ser Asp
            210                 215                 220
cat ggg atg acc cag tgt tct cag gac aga ctg ata aac ctg gat tcc   828
His Gly Met Thr Gln Cys Ser Gln Asp Arg Leu Ile Asn Leu Asp Ser
        225                 230                 235
tgc atc gat cat tca tac tac act ctt ata gat ttg agc cca gtt gct   876
Cys Ile Asp His Ser Tyr Tyr Thr Leu Ile Asp Leu Ser Pro Val Ala
    240                 245                 250
gca ata ctt ccc aaa ata aat aga aca gag gtt tat aac aaa ctg aaa   924
Ala Ile Leu Pro Lys Ile Asn Arg Thr Glu Val Tyr Asn Lys Leu Lys
255                 260                 265                 270
aac tgt agc cct cat atg aat gtt tat ctc aaa gaa gac att cct aac   972
Asn Cys Ser Pro His Met Asn Val Tyr Leu Lys Glu Asp Ile Pro Asn
                275                 280                 285
aga ttt tat tac caa cat aat gat cga att cag ccc att att ttg gtt  1020
Arg Phe Tyr Tyr Gln His Asn Asp Arg Ile Gln Pro Ile Ile Leu Val
            290                 295                 300
gcc gat gaa ggc tgg aca att gtg cta aat gaa tca tca caa aan tta  1068
Ala Asp Glu Gly Trp Thr Ile Val Leu Asn Glu Ser Ser Gln Lys Leu
        305                 310                 315
ggt gac cat ggt tat gat aat tct ttg cct agt atg cat cca ttt cta  1116
Gly Asp His Gly Tyr Asp Asn Ser Leu Pro Ser Met His Pro Phe Leu
    320                 325                 330
gct gcc cac gga cct gca ttt cac aaa ggc tac aag cat agc aca att  1164
Ala Ala His Gly Pro Ala Phe His Lys Gly Tyr Lys His Ser Thr Ile
335                 340                 345                 350
aac att gtg gat att tat cca atg atg tgc cac atc ctg gga tta aaa  1212
Asn Ile Val Asp Ile Tyr Pro Met Met Cys His Ile Leu Gly Leu Lys
                355                 360                 365
cca cat ccc aat aat ggg acc ttt ggt cat act aag tgc ttg tta gtt  1260
Pro His Pro Asn Asn Gly Thr Phe Gly His Thr Lys Cys Leu Leu Val
            370                 375                 380
gac cag tgg tgc att aat ctc cca gaa gcc atc gcg att gtt atc ggt  1308
Asp Gln Trp Cys Ile Asn Leu Pro Glu Ala Ile Ala Ile Val Ile Gly
        385                 390                 395
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tca ctc ttg gtg tta acc atg cta aca tgc ctc ata ata atc atg cag 1356
Ser Leu Leu Val Leu Thr Met Leu Thr Cys Leu Ile Ile Ile Met Gln
400 405 410
aat aga ctt tct gta cct cgt cca ttt tct cga ctt cag cta caa gaa 1404
Asn Arg Leu Ser Val Pro Arg Pro Phe Ser Arg Leu Gln Leu Gln Glu
415 420 425 430
gat gat gat gat ccc tta att ggg tgacatgtgc tagggcttat acaaagtgtc 1458
Asp Asp Asp Asp Pro Leu Ile Gly
435
tttgattaat cacaaaacta agaatacatc caaagaatag tgttgtaact atgaaaaaga 1518
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aatgaagaaa tattttaagg aaacctattt gaaaaaaaaa aacaaa 2044

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Cys Thr Cys Glu Ile Arg Pro Trp Phe Thr Pro Arg Ser Ile Tyr Met
15 20 25
Glu Ala Ser Thr Val Asp Cys Asn Asp Leu Gly Leu Leu Thr Phe Pro
30 35 40
Ala Arg Leu Pro Ala Asn Thr Gln Ile Leu Leu Leu Gln Thr Asn Asn
45 50 55

Ile Ala Lys Ile Glu Tyr Ser Thr Asp Phe Pro Val Asn Leu Thr Gly
60 65 70

Leu Asp Leu Ser Gln Asn Asn Leu Ser Ser Val Thr Asn Ile Asn Val
75 80 85 90

Lys Lys Met Pro Gln Leu Leu Ser Val Tyr Leu Glu Glu Asn Lys Leu
95 100 105

Thr Glu Leu Pro Glu Lys Cys Leu Ser Glu Leu Ser Asn Leu Gln Glu
110 115 120

Leu Tyr Ile Asn His Asn Leu Leu Ser Thr Ile Ser Pro Gly Ala Phe
125 130 135

Ile Gly Leu His Asn Leu Leu Arg Leu His Leu Asn Ser Asn Arg Leu
140 145 150

Gln Met Ile Asn Ser Lys Trp Phe Asp Ala Leu Pro Asn Leu Glu Ile
155 160 165 170

Leu Met Ile Gly Glu Asn Pro Ile Ile Arg Ile Lys Asp Met Asn Phe
175 180 185

Lys Pro Leu Ile Asn Leu Arg Ser Leu Val Ile Ala Gly Ile Asn Leu
190 195 200

Thr Glu Ile Pro Asp Asn Ala Leu Val Gly Leu Glu Asn Leu Glu Ser
205 210 215

Ile Ser Phe Tyr Asp Asn Arg Leu Ile Lys Val Pro His Val Ala Leu
220 225 230

Gln Lys Val Val Asn Leu Lys Phe Leu Asp Leu Asn Lys Asn Pro Ile
235 240 245 250

Asn Arg Ile Arg Arg Gly Asp Phe Ser Asn Met Leu His Leu Lys Glu
255 260 265

Leu Gly Ile Asn Asn Met Pro Glu Leu Ile Ser Ile Asp Ser Leu Ala
270 275 280

Val Asp Asn Leu Pro Asp Leu Arg Lys Ile Glu Ala Thr Asn Asn Pro
285 290 295

Arg Leu Ser Tyr Ile His Pro Asn Ala Phe Phe Arg Leu Pro Lys Leu
300 305 310

Glu Ser Leu Met Leu Asn Ser Asn Ala Leu Ser Ala Leu Tyr His Gly
315 320 325 330

Thr Ile Glu Ser Leu Pro Asn Leu Lys Glu Ile Ser Ile His Ser Asn
335 340 345

Pro Ile Arg Cys Asp Cys Val Ile Arg Trp Met Asn Met Asn Lys Thr
350 355 360

Asn Ile Arg Phe Met Glu Pro Asp Ser Leu Phe Cys Val Asp Pro Pro
365 370 375

Glu Phe Gln Gly Gln Asn Val Arg Gln Val His Phe Arg Asp Met Met
380 385 390

Glu Ile Cys Leu Pro Leu Ile Ala Pro Glu Ser Phe Pro Ser Asn Leu
395 400 405 410

Asn Val Glu Ala Gly Ser Tyr Val Ser Phe His Cys Arg Ala Thr Ala
415 420 425

Glu Pro Gln Pro Glu Ile Tyr Trp Ile Thr Pro Ser Gly Gln Lys Leu
430 435 440

Leu Pro Asn Thr Leu Thr Asp Lys Phe Tyr Val His Ser Glu Gly Thr
445 450 455

Leu Asp Ile Asn Gly Val Thr Pro Lys Glu Gly Gly Leu Tyr Thr Cys
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Ile Ala Thr Asn Leu Val Gly Ala Asp Leu Lys Ser Val Met Ile Lys
475 480 485 490

Val Asp Gly Ser Phe Pro Gln Asp Asn Asn Gly Ser Leu Asn Ile Lys
495 500 505

Ile Arg Asp Ile Gln Ala Asn Ser Val Leu Val Ser Trp Lys Ala Ser
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Ser Lys Ile Leu Lys Ser Ser Val Lys Trp Thr Ala Phe Val Lys Thr
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Glu Asn Ser His Ala Ala Gln Ser Ala Arg Ile Pro Ser Asp Val Lys
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Val Tyr Asn Leu Thr His Leu Asn Pro Ser Thr Glu Tyr Lys Ile Cys
555 560 565 570

Ile Asp Ile Pro Thr Ile Tyr Gln Lys Asn Arg Lys Lys Cys Val Asn
575 580 585

Val Thr Thr Lys Gly Leu His Pro Asp Gln Lys Glu Tyr Glu Lys Asn
590 595 600

Asn Thr Thr Thr Leu Met Ala Cys Leu Gly Gly Leu Leu Gly Ile Ile
605 610 615

Gly Val Ile Cys Leu Ile Ser Cys Leu Ser Pro Glu Met Asn Cys Asp
620 625 630

Gly Gly His Ser Tyr Val Arg Asn Tyr Leu Gln Lys Pro Thr Phe Ala
635 640 645 650

Leu Gly Glu Leu Tyr Pro Pro Leu Ile Asn Leu Trp Glu Ala Gly Lys
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Glu Lys Ser Thr Ser Leu Lys Val Lys Ala Thr Val Ile Gly Leu Pro
670 675 680

Thr Asn Met Ser
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MeT
-22

aag gac atg cca ctc cga att cat gtg cta ctt ggc cta gct atc act 944
Lys Asp Met Pro Leu Arg Ile His Val Leu Leu Gly Leu Ala Ile Thr
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aca cta gta caa gct gta gat aaa aaa gtg gat tgt cca cgg tta tgt 992
Thr Leu Val Gln Ala Val Asp Lys Lys Val Asp Cys Pro Arg Leu Cys
-5 1 5 10

acg tgt gaa atc agg cct tgg ttt aca ccc aga tcc att tat atg gaa 1040
Thr Cys Glu Ile Arg Pro Trp Phe Thr Pro Arg Ser Ile Tyr Met Glu
15 20 25

gca tct aca gtg gat tgt aat gat tta ggt ctt tta act ttc cca gcc 1088
Ala Ser Thr Val Asp Cys Asn Asp Leu Gly Leu Leu Thr Phe Pro Ala
30 35 40

aga ttg cca gct aac aca cag att ctt ctc cta cag act aac aat att 1136
Arg Leu Pro Ala Asn Thr Gln Ile Leu Leu Leu Gln Thr Asn Asn Ile
45 50 55

gca aaa att gaa tac tcc aca gac ttt cca gta aac ctt act ggc ctg 1184
Ala Lys Ile Glu Tyr Ser Thr Asp Phe Pro Val Asn Leu Thr Gly Leu
60 65 70 75

gat tta tct caa aac aat tta tct tca gtc acc aat att aat gta aaa 1232
Asp Leu Ser Gln Asn Asn Leu Ser Ser Val Thr Asn Ile Asn Val Lys
80 85 90

aag atg cct cag ctc ctt tct gtg tac cta gag gaa aac aaa ctt act 1280
Lys Met Pro Gln Leu Leu Ser Val Tyr Leu Glu Glu Asn Lys Leu Thr
95 100 105

gaa ctg cct gaa aaa tgt ctg tcc gaa ctg agc aac tta caa gaa ctc 1328
Glu Leu Pro Glu Lys Cys Leu Ser Glu Leu Ser Asn Leu Gln Glu Leu
110 115 120

tat att aat cac aac ttg ctt tct aca att tca cct gga gcc ttt att 1376
Tyr Ile Asn His Asn Leu Leu Ser Thr Ile Ser Pro Gly Ala Phe Ile
125 130 135

ggc cta cat aat ctt ctt cga ctt cat ctc aat tca aat aga ttg cag 1424
Gly Leu His Asn Leu Leu Arg Leu His Leu Asn Ser Asn Arg Leu Gln
140 145 150 155

atg atc aac agt aag tgg ttt gat gct ctt cca aat cta gag att ctg 1472
Met Ile Asn Ser Lys Trp Phe Asp Ala Leu Pro Asn Leu Glu Ile Leu
160 165 170

atg att ggg gaa aat cca att atc aga atc aaa gac atg aac ttt aag 1520
Met Ile Gly Glu Asn Pro Ile Ile Arg Ile Lys Asp Met Asn Phe Lys
175 180 185

cct ctt atc aat ctt cgc agc ctg gtt ata gct ggt ata aac ctc aca 1568
Pro Leu Ile Asn Leu Arg Ser Leu Val Ile Ala Gly Ile Asn Leu Thr
190 195 200

gaa ata cca gat aac gcc ttg gtt gga ctg gaa aac tta gaa agc atc 1616
Glu Ile Pro Asp Asn Ala Leu Val Gly Leu Glu Asn Leu Glu Ser Ile
205 210 215

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Ser Phe Tyr Asp Asn Arg Leu Ile Lys Val Pro His Val Ala Leu Gln
220 225 230 235

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Lys Val Val Asn Leu Lys Phe Leu Asp Leu Asn Lys Asn Pro Ile Asn
240 245 250

aga ata cga agg ggt gat ttt agc aat atg cta cac tta aaa gag ttg 1760
Arg Ile Arg Arg Gly Asp Phe Ser Asn Met Leu His Leu Lys Glu Leu
255 260 265

ggg ata aat aat atg cct gag ctg att tcc atc gat agt ctt gct gtg 1808
Gly Ile Asn Asn Met Pro Glu Leu Ile Ser Ile Asp Ser Leu Ala Val
270 275 280

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gat aac ctg cca gat tta aga aaa ata gaa gct act aac aac cct aga  1856
Asp Asn Leu Pro Asp Leu Arg Lys Ile Glu Ala Thr Asn Asn Pro Arg
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ttg tct tac att cac ccc aat gca ttt ttc aga ctc ccc aag ctg gaa  1904
Leu Ser Tyr Ile His Pro Asn Ala Phe Phe Arg Leu Pro Lys Leu Glu
300                 305                 310                 315

tca ctc atg ctg aac agc aat gct ctc agt gcc ctg tac cat ggt acc  1952
Ser Leu Met Leu Asn Ser Asn Ala Leu Ser Ala Leu Tyr His Gly Thr
                320                 325                 330

att gag tct ctg cca aac ctc aag gaa atc agc ata cac agt aac ccc  2000
Ile Glu Ser Leu Pro Asn Leu Lys Glu Ile Ser Ile His Ser Asn Pro
            335                 340                 345

atc agg tgt gac tgt gtc atc cgt tgg atg aac atg aac aaa acc aac  2048
Ile Arg Cys Asp Cys Val Ile Arg Trp Met Asn Met Asn Lys Thr Asn
        350                 355                 360

att cga ttc atg gag cca gat tca ctg ttt tgc gtg gac cca cct gaa  2096
Ile Arg Phe Met Glu Pro Asp Ser Leu Phe Cys Val Asp Pro Pro Glu
    365                 370                 375

ttc caa ggt cag aat gtt cgg caa gtg cat ttc agg gac atg atg gaa  2144
Phe Gln Gly Gln Asn Val Arg Gln Val His Phe Arg Asp Met Met Glu
380                 385                 390                 395

att tgt ctc cct ctt ata gct cct gag agc ttt cct tct aat cta aat  2192
Ile Cys Leu Pro Leu Ile Ala Pro Glu Ser Phe Pro Ser Asn Leu Asn
                400                 405                 410

gta gaa gct ggg agc tat gtt tcc ttt cac tgt aga gct act gca gaa  2240
Val Glu Ala Gly Ser Tyr Val Ser Phe His Cys Arg Ala Thr Ala Glu
            415                 420                 425

cca cag cct gaa atc tac tgg ata aca cct tct ggt caa aaa ctc ttg  2288
Pro Gln Pro Glu Ile Tyr Trp Ile Thr Pro Ser Gly Gln Lys Leu Leu
        430                 435                 440

cct aat acc ctg aca gac aag ttc tat gtc cat tct gag gga aca cta  2336
Pro Asn Thr Leu Thr Asp Lys Phe Tyr Val His Ser Glu Gly Thr Leu
    445                 450                 455

gat ata aat ggc gta act ccc aaa gaa ggg ggt tta tat act tgt ata  2384
Asp Ile Asn Gly Val Thr Pro Lys Glu Gly Gly Leu Tyr Thr Cys Ile
460                 465                 470                 475
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gca act aac cta gtt ggc gct gac ttg aag tct gtt atg atc aaa gtg 2432
Ala Thr Asn Leu Val Gly Ala Asp Leu Lys Ser Val Met Ile Lys Val
480 485 490

gat gga tct ttt cca caa gat aac aat ggc tct ttg aat att aaa ata 2480
Asp Gly Ser Phe Pro Gln Asp Asn Asn Gly Ser Leu Asn Ile Lys Ile
495 500 505

aga gat att cag gcc aat tca gtt ttg gtg tcc tgg aaa gca agt tct 2528
Arg Asp Ile Gln Ala Asn Ser Val Leu Val Ser Trp Lys Ala Ser Ser
510 515 520

aaa att ctc aaa tct agt gtt aaa tgg aca gcc ttt gtc aag act gaa 2576
Lys Ile Leu Lys Ser Ser Val Lys Trp Thr Ala Phe Val Lys Thr Glu
525 530 535

aat tct cat gct gcg caa agt gct cga ata cca tct gat gtc aag gta 2624
Asn Ser His Ala Ala Gln Ser Ala Arg Ile Pro Ser Asp Val Lys Val
540 545 550 555

tat aat ctt act cat ctg aat cca tca act gag tat aaa att tgt att 2672
Tyr Asn Leu Thr His Leu Asn Pro Ser Thr Glu Tyr Lys Ile Cys Ile
560 565 570

gat att ccc acc atc tat cag aaa aac aga aaa aaa tgt gta aat gtc 2720
Asp Ile Pro Thr Ile Tyr Gln Lys Asn Arg Lys Lys Cys Val Asn Val
575 580 585

acc acc aaa ggt ttg cac cct gat caa aaa gag tat gaa aag aat aat 2768
Thr Thr Lys Gly Leu His Pro Asp Gln Lys Glu Tyr Glu Lys Asn Asn
590 595 600

acc aca aca ctt atg gcc tgt ctt gga ggc ctt ctg ggg att att ggt 2816
Thr Thr Thr Leu Met Ala Cys Leu Gly Gly Leu Leu Gly Ile Ile Gly
605 610 615

gtg ata tgt ctt atc agc tgc ctc tct cca gaa atg aac tgt gat ggt 2864
Val Ile Cys Leu Ile Ser Cys Leu Ser Pro Glu Met Asn Cys Asp Gly
620 625 630 635

gga cac agc tat gtg agg aat tac tta cag aaa cca acc ttt gca tta 2912
Gly His Ser Tyr Val Arg Asn Tyr Leu Gln Lys Pro Thr Phe Ala Leu
640 645 650

ggt gag ctt tat cct cct ctg ata aat ctc tgg gaa gca gga aaa gaa 2960
Gly Glu Leu Tyr Pro Pro Leu Ile Asn Leu Trp Glu Ala Gly Lys Glu
655 660 665

aaa agt aca tca ctg aaa gta aaa gca act gtt ata ggt tta cca aca 3008
Lys Ser Thr Ser Leu Lys Val Lys Ala Thr Val Ile Gly Leu Pro Thr
670 675 680

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Asn Met Ser
685

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<212> PRT
<213> Homo sapiens

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Arg Arg Arg Leu Leu His Lys Asp Gly Ser Cys Asn Val Tyr Phe Lys
35 40 45
His Ile Phe Gly Glu Trp Gly Ser Tyr Val Val Asp Ile Phe Thr Thr
50 55 60
Leu Val Asp Thr Lys Trp Arg His Met Phe Val Ile Phe Ser Leu Ser
65 70 75 80
Tyr Ile Leu Ser Trp Leu Ile Phe Gly Ser Val Phe Trp Leu Ile Ala
85 90 95
Phe His His Gly Asp Leu Leu Asn Asp Pro Asp Ile Thr Pro Cys Val
100 105 110
Asp Asn Val His Ser Phe Thr Gly Ala Phe Leu Phe Ser Leu Glu Thr
115 120 125
Gln Thr Thr Ile Gly Tyr Gly Tyr Arg Cys Val Thr Glu Glu Cys Ser
130 135 140
Val Ala Val Leu Met Val Ile Leu Gln Ser Ile Leu Ser Cys Ile Ile
145 150 155 160
Asn Thr Phe Ile Ile Gly Ala Ala Leu Ala Lys Met Ala Thr Ala Arg
165 170 175

Lys Arg Ala Gln Thr Ile Arg Phe Ser Tyr Phe Ala Leu Ile Gly Met
180 185 190

Arg Asp Gly Lys Leu Cys Leu Met Trp Arg Ile Gly Asp Phe Arg Pro
195 200 205

Asn His Val Val Glu Gly Thr Val Arg Ala Gln Leu Leu Arg Tyr Thr
210 215 220

Glu Asp Ser Glu Gly Arg Met Thr Met Ala Phe Lys Asp Leu Lys Leu
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<213> Homo sapiens

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ggcagctgta atgtctactt caagcacatt tttggagaat ggggaagcta tgtggttgac 180
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gaagaatgtt ctgtggccgt gctcatggtg atcctccagt ccatcttaag ttgcatcata 480
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accattcgtt tcagctactt tgcacttata ggtatgagag atgggaagct ttgcctcatg 600
tggcgcattg gtgatttttcg gccaaaccac gtggtagaag gaacagttag agcccaactt 660
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Met Ser Tyr Tyr Gly Ser Ser Tyr His Ile Ile
1 5 10

aat gcg gac gca aaa tac cca ggc tac ccg cca gag cac att ata gct 158
Asn Ala Asp Ala Lys Tyr Pro Gly Tyr Pro Pro Glu His Ile Ile Ala
15 20 25

gag aag aga aga gca aga aga cga tta ctt cac aaa gat ggc agc tgt 206
Glu Lys Arg Arg Ala Arg Arg Arg Leu Leu His Lys Asp Gly Ser Cys
30 35 40

aat gtc tac ttc aag cac att ttt gga gaa tgg gga agc tat gtg gtt 254
Asn Val Tyr Phe Lys His Ile Phe Gly Glu Trp Gly Ser Tyr Val Val
45 50 55

gac atc ttc acc act ctt gtg gac acc aag tgg cgc cat atg ttt gtg 302
Asp Ile Phe Thr Thr Leu Val Asp Thr Lys Trp Arg His Met Phe Val
60 65 70 75

ata ttt tct tta tct tat att ctc tcg tgg ttg ata ttt ggc tct gtc 350
Ile Phe Ser Leu Ser Tyr Ile Leu Ser Trp Leu Ile Phe Gly Ser Val
80 85 90

ttt tgg ctc ata gcc ttt cat cat ggc gat cta tta aat gat cca gac 398
Phe Trp Leu Ile Ala Phe His His Gly Asp Leu Leu Asn Asp Pro Asp
95 100 105

atc aca cct tgt gtt gac aac gtc cat tct ttc aca ggg gcc ttt ttg 446
Ile Thr Pro Cys Val Asp Asn Val His Ser Phe Thr Gly Ala Phe Leu
110 115 120

ttc tcc cta gag acc caa acc acc ata gga tat ggt tat cgc tgt gtt 494
Phe Ser Leu Glu Thr Gln Thr Thr Ile Gly Tyr Gly Tyr Arg Cys Val
125 130 135

act gaa gaa tgt tct gtg gcc gtg ctc atg gtg atc ctc cag tcc atc 542
Thr Glu Glu Cys Ser Val Ala Val Leu Met Val Ile Leu Gln Ser Ile
140 145 150 155

tta agt tgc atc ata aat acc ttt atc att gga gct gcc ttg gcc aaa 590
Leu Ser Cys Ile Ile Asn Thr Phe Ile Ile Gly Ala Ala Leu Ala Lys
160 165 170

atg gca act gct cga aag aga gcc caa acc att cgt ttc agc tac ttt 638
Met Ala Thr Ala Arg Lys Arg Ala Gln Thr Ile Arg Phe Ser Tyr Phe
175 180 185

gca ctt ata ggt atg aga gat ggg aag ctt tgc ctc atg tgg cgc att 686
Ala Leu Ile Gly Met Arg Asp Gly Lys Leu Cys Leu Met Trp Arg Ile
190 195 200

ggt gat ttt cgg cca aac cac gtg gta gaa gga aca gtt aga gcc caa 734
Gly Asp Phe Arg Pro Asn His Val Val Glu Gly Thr Val Arg Ala Gln
205 210 215

ctt ctc cgc tat aca gaa gac agt gaa ggg agg atg acg atg gca ttt 782
Leu Leu Arg Tyr Thr Glu Asp Ser Glu Gly Arg Met Thr Met Ala Phe
220 225 230 235

aaa gac ctc aaa tta gtc aac gac caa atc atc ctg gtc acc ccg gta 830
Lys Asp Leu Lys Leu Val Asn Asp Gln Ile Ile Leu Val Thr Pro Val
240 245 250

act att gtc cca tgaccctgcc aaatcccccc ctgtgagaaa cacccaaaaa 882
Thr Ile Val Pro
255

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-10 -5 1 5
Glu His Ser Glu Asn Val His Ile Ser Gly Val Ser Thr Ala Cys Gly
10 15 20
Glu Thr Pro Glu Gln Ile Arg Ala Pro Ser Gly Ile Ile Thr Ser Pro

25 30 35

Gly Trp Pro Ser Glu Tyr Pro Ala Lys Ile Asn Cys Ser Trp Phe Ile

40 45 50

Arg Ala Asn Pro Gly Glu Ile Ile Thr Ile Ser Phe Gln Asp Phe Asp

55 60 65

Ile Gln Gly Ser Arg Arg Cys Asn Leu Asp Trp Leu Thr Ile Glu Thr

70 75 80 85

Tyr Lys Asn Ile Glu Ser Tyr Arg Ala Cys Gly Ser Thr Ile Pro Pro

90 95 100

Pro Tyr Ile Ser Ser Gln Asp His Ile Trp Ile Arg Phe His Ser Asp

105 110 115

Asp Asn Ile Ser Arg Lys Gly Phe Arg Leu Ala Tyr Phe Ser Gly Lys

120 125 130

Ser Glu Glu Pro Asn Cys Ala Cys Asp Gln Phe Arg Cys Gly Asn Gly

135 140 145

Lys Cys Ile Pro Glu Ala Trp Lys Cys Asn Asn Met Asp Glu Cys Gly

150 155 160 165

Asp Ser Ser Asp Glu Glu Ile Cys Ala Lys Glu Ala Asn Pro Pro Thr

170 175 180

Ala Ala Ala Phe Gln Pro Cys Ala Tyr Asn Gln Phe Gln Cys Leu Ser

185 190 195

Arg Phe Thr Lys Val Tyr Thr Cys Leu Pro Glu Ser Leu Lys Cys Asp

200 205 210

Gly Asn Ile Asp Cys Leu Asp Leu Gly Asp Glu Ile Asp Cys Asp Val

215 220 225

Pro Thr Cys Gly Gln Trp Leu Lys Tyr Phe Tyr Gly Thr Phe Asn Ser

230 235 240 245

Pro Asn Tyr Pro Asp Phe Tyr Pro Pro Gly Ser Asn Cys Thr Trp Leu

250 255 260

Ile Asp Thr Gly Asp His Arg Lys Val Ile Leu Arg Phe Thr Asp Phe

265 270 275

Lys Leu Asp Gly Thr Gly Tyr Gly Asp Tyr Val Lys Ile Tyr Asp Gly

280 285 290

Leu Glu Glu Asn Pro His Lys Leu Leu Arg Val Leu Thr Ala Phe Asp

295 300 305

Ser His Ala Pro Leu Thr Val Val Ser Ser Ser Gly Gln Ile Arg Val

310 315 320 325
His Phe Cys Ala Asp Lys Val Asn Ala Ala Arg Gly Phe Asn Ala Thr
330 335 340
Tyr Gln Val Asp Gly Phe Cys Leu Pro Trp Glu Ile Pro Cys Gly Gly
345 350 355
Asn Trp Gly Cys Tyr Thr Glu Gln Gln Arg Cys Asp Gly Tyr Trp His
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Cys Pro Asn Gly Arg Asp Glu Thr Asn Cys Thr Met Cys Gln Lys Glu
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Glu Phe Pro Cys Ser Arg Asn Gly Val Cys Tyr Pro Arg Ser Asp Arg
390 395 400 405
Cys Asn Tyr Gln Asn His Cys Pro Asn Gly Ser Asp Glu Lys Asn Cys
410 415 420
Phe Phe Cys Gln Pro Gly Asn Phe His Cys Lys Asn Asn Arg Cys Val
425 430 435
Phe Glu Ser Trp Val Cys Asp Ser Gln Asp Asp Cys Gly Asp Gly Ser
440 445 450
Asp Glu Glu Asn Cys Pro Val Ile Val Pro Thr Arg Val Ile Thr Ala
455 460 465
Ala Val Ile Gly Ser Leu Ile Cys Gly Leu Leu Leu Val Ile Ala Leu
470 475 480 485
Gly Cys Thr Cys Lys Leu Tyr Ser Leu Arg Met Phe Glu Arg Arg Ser
490 495 500
Phe Glu Thr Gln Leu Ser Arg Val Glu Ala Glu Leu Leu Arg Arg Glu
505 510 515
Ala Pro Pro Ser Tyr Gly Gln Leu Ile Ala Gln Gly Leu Ile Pro Pro
520 525 530
Val Glu Asp Phe Pro Val Cys Ser Pro Asn Gln Ala Ser Val Leu Glu
535 540 545
Asn Leu Arg Leu Ala Val Arg Ser Gln Leu Gly Phe Thr Ser Val Arg
550 555 560 565
Leu Pro Met Ala Gly Arg Ser Ser Asn Ile Trp Asn Arg Ile Phe Asn
570 575 580
Phe Ala Arg Ser Arg His Ser Gly Ser Leu Ala Leu Val Ser Ala Asp
585 590 595
Gly Asp Glu Val Val Pro Ser Gln Ser Thr Ser Arg Glu Pro Glu Arg

600 605 610

Asn His Thr His Arg Ser Leu Phe Ser Val Glu Ser Asp Asp Thr Asp

615 620 625

Thr Glu Asn Glu Arg Arg Asp Met Ala Gly Ala Ser Gly Gly Val Ala

630 635 640 645

Ala Pro Leu Pro Gln Lys Val Pro Pro Thr Thr Ala Val Glu Ala Thr

650 655 660

Val Gly Ala Cys Ala Ser Ser Ser Thr Gln Ser Thr Arg Gly Gly His

665 670 675

Ala Asp Asn Gly Arg Asp Val Thr Ser Val Glu Pro Pro Ser Val Ser

680 685 690

Pro Ala Arg His Gln Leu Thr Ser Ala Leu Ser Arg Met Thr Gln Gly

695 700 705

Leu Arg Trp Val Arg Phe Thr Leu Gly Arg Ser Ser Ser Leu Ser Gln

710 715 720 725

Asn Gln Ser Pro Leu Arg Gln Leu Asp Asn Gly Val Ser Gly Arg Glu

730 735 740

Asp Asp Asp Asp Val Glu Met Leu Ile Pro Ile Ser Asp Gly Ser Ser

745 750 755

Asp Phe Asp Val Asn Asp Cys Ser Arg Pro Leu Leu Asp Leu Ala Ser

760 765 770

Asp Gln Gly Gln Gly Leu Arg Gln Pro Tyr Asn Ala Thr Asn Pro Gly

775 780 785

Val Arg Pro Ser Asn Arg Asp Gly Pro Cys Glu Arg Cys Gly Ile Val

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825 830

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Ser Thr Lys Glu Ser Pro Arg Trp Arg Ser Ala Leu Leu Leu Leu Phe
-20 -15 -10

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Ile Arg Ala Pro Ser Gly Ile Ile Thr Ser Pro Gly Trp Pro Ser Glu
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tat cct gca aaa atc aac tgt agc tgg ttc ata agg gca aac cca ggc   295
Tyr Pro Ala Lys Ile Asn Cys Ser Trp Phe Ile Arg Ala Asn Pro Gly
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gaa atc att act ata agt ttt cag gat ttt gat att caa gga tcc aga   343
Glu Ile Ile Thr Ile Ser Phe Gln Asp Phe Asp Ile Gln Gly Ser Arg
      60                  65                  70
agg tgc aat ttg gac tgg ttg aca ata gaa aca tac aag aat att gaa   391
Arg Cys Asn Leu Asp Trp Leu Thr Ile Glu Thr Tyr Lys Asn Ile Glu
  75                  80                  85                  90
agt tac aga gct tgt ggt tcc aca att cca cct ccg tat atc tct tca   439
Ser Tyr Arg Ala Cys Gly Ser Thr Ile Pro Pro Pro Tyr Ile Ser Ser
                  95                 100                 105
caa gac cac atc tgg att agg ttt cat tcg gat gac aac atc tct aga   487
Gln Asp His Ile Trp Ile Arg Phe His Ser Asp Asp Asn Ile Ser Arg
              110                 115                 120
aag ggt ttc aga ctg gca tat ttt tca ggg aaa tct gag gaa cca aat   535
Lys Gly Phe Arg Leu Ala Tyr Phe Ser Gly Lys Ser Glu Glu Pro Asn
          125                 130                 135
tgt gct tgt gat cag ttt cgt tgt ggt aat gga aag tgt ata cca gaa   583
Cys Ala Cys Asp Gln Phe Arg Cys Gly Asn Gly Lys Cys Ile Pro Glu
      140                 145                 150
gcc tgg aaa tgt aat aac atg gat gaa tgt gga gat agt tcc gat gaa   631
Ala Trp Lys Cys Asn Asn Met Asp Glu Cys Gly Asp Ser Ser Asp Glu
  155                 160                 165                 170
gag atc tgt gcc aaa gaa gca aat cct cca act gct gct gct ttt caa   679
Glu Ile Cys Ala Lys Glu Ala Asn Pro Pro Thr Ala Ala Ala Phe Gln
                  175                 180                 185
ccc tgt gct tac aac cag ttc cag tgt ttg tcc cgt ttt acc aaa gtt   727
Pro Cys Ala Tyr Asn Gln Phe Gln Cys Leu Ser Arg Phe Thr Lys Val
              190                 195                 200
tac act tgc ctc ccc gaa tct ttg aaa tgt gat ggg aac att gac tgc   775
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Leu Asp Leu Gly Asp Glu Ile Asp Cys Asp Val Pro Thr Cys Gly Gln
   220                 225                 230
tgg cta aaa tat ttt tat ggt act ttt aat tct ccc aat tat cca gac   871
Trp Leu Lys Tyr Phe Tyr Gly Thr Phe Asn Ser Pro Asn Tyr Pro Asp
235                 240                 245                 250
ttt tat cct cct gga agc aat tgc acc tgg tta ata gac act ggt gat   919
Phe Tyr Pro Pro Gly Ser Asn Cys Thr Trp Leu Ile Asp Thr Gly Asp
                255                 260                 265
cac cgt aaa gtc att tta cgc ttc act gac ttt aaa ctt gat ggt act   967
His Arg Lys Val Ile Leu Arg Phe Thr Asp Phe Lys Leu Asp Gly Thr
            270                 275                 280
ggt tat ggt gat tat gtc aaa ata tat gat gga tta gag gag aat cca  1015
Gly Tyr Gly Asp Tyr Val Lys Ile Tyr Asp Gly Leu Glu Glu Asn Pro
      285                 290                 295
cac aag ctt ttg cgt gtg ttg aca gct ttt gat tct cat gca cct ctt  1063
His Lys Leu Leu Arg Val Leu Thr Ala Phe Asp Ser His Ala Pro Leu
   300                 305                 310
aca gtt gtt tct tct tct gga cag ata agg gta cat ttt tgt gct gat  1111
Thr Val Val Ser Ser Ser Gly Gln Ile Arg Val His Phe Cys Ala Asp
315                 320                 325                 330
aaa gtg aat gct gca agg gga ttt aat gct act tac caa gta gat ggg  1159
Lys Val Asn Ala Ala Arg Gly Phe Asn Ala Thr Tyr Gln Val Asp Gly
                335                 340                 345
ttc tgt ttg cca tgg gaa ata ccc tgt gga ggt aac tgg ggg tgt tat  1207
Phe Cys Leu Pro Trp Glu Ile Pro Cys Gly Gly Asn Trp Gly Cys Tyr
            350                 355                 360
act gag cag cag cgt tgt gat ggg tat tgg cat tgc cca aat gga agg  1255
Thr Glu Gln Gln Arg Cys Asp Gly Tyr Trp His Cys Pro Asn Gly Arg
      365                 370                 375
gat gaa acc aat tgt acc atg tgc cag aag gaa gaa ttt cca tgt tcc  1303
Asp Glu Thr Asn Cys Thr Met Cys Gln Lys Glu Glu Phe Pro Cys Ser
   380                 385                 390
cga aat ggt gtc tgt tat cct cgt tct gat cgc tgc aac tac cag aat  1351
```

```
Arg Asn Gly Val Cys Tyr Pro Arg Ser Asp Arg Cys Asn Tyr Gln Asn
395                 400                 405                 410

cat tgc cca aat ggc tca gat gaa aaa aac tgc ttt ttt tgc caa cca  1399
His Cys Pro Asn Gly Ser Asp Glu Lys Asn Cys Phe Phe Cys Gln Pro
                415                 420                 425

gga aat ttc cat tgt aaa aac aat cgt tgt gtg ttt gaa agt tgg gtg  1447
Gly Asn Phe His Cys Lys Asn Asn Arg Cys Val Phe Glu Ser Trp Val
            430                 435                 440

tgt gat tct caa gat gac tgt ggt gat ggc agc gat gaa gaa aat tgc  1495
Cys Asp Ser Gln Asp Asp Cys Gly Asp Gly Ser Asp Glu Glu Asn Cys
        445                 450                 455

cca gta atc gtg cct aca aga gtc atc act gct gcc gtc ata ggg agc  1543
Pro Val Ile Val Pro Thr Arg Val Ile Thr Ala Ala Val Ile Gly Ser
    460                 465                 470

ctc atc tgt ggc ctg tta ctc gtc ata gca ttg gga tgt act tgt aag  1591
Leu Ile Cys Gly Leu Leu Leu Val Ile Ala Leu Gly Cys Thr Cys Lys
475                 480                 485                 490

ctt tat tct ctg aga atg ttt gaa aga aga tca ttt gaa aca cag ttg  1639
Leu Tyr Ser Leu Arg Met Phe Glu Arg Arg Ser Phe Glu Thr Gln Leu
                495                 500                 505

tca aga gtg gaa gca gaa ttg tta aga aga gaa gct cct ccc tcg tat  1687
Ser Arg Val Glu Ala Glu Leu Leu Arg Arg Glu Ala Pro Pro Ser Tyr
            510                 515                 520

gga caa ttg att gct cag ggt tta att cca cca gtt gaa gat ttt cct  1735
Gly Gln Leu Ile Ala Gln Gly Leu Ile Pro Pro Val Glu Asp Phe Pro
        525                 530                 535

gtt tgt tca cct aat cag gct tct gtt ttg gaa aat ctg agg cta gcg  1783
Val Cys Ser Pro Asn Gln Ala Ser Val Leu Glu Asn Leu Arg Leu Ala
    540                 545                 550

gta cga tct cag ctt gga ttt act tca gtc agg ctt cct atg gca ggc  1831
Val Arg Ser Gln Leu Gly Phe Thr Ser Val Arg Leu Pro Met Ala Gly
555                 560                 565                 570

aga tca agc aac att tgg aac cgt att ttt aat ttt gca aga tca cgt  1879
Arg Ser Ser Asn Ile Trp Asn Arg Ile Phe Asn Phe Ala Arg Ser Arg
                575                 580                 585

cat tct ggg tca ttg gct ttg gtc tca gca gat gga gat gag gtt gtc  1927
```

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His Ser Gly Ser Leu Ala Leu Val Ser Ala Asp Gly Asp Glu Val Val
                590                 595                 600

cct agt cag agt acc agt aga gaa cct gag aga aat cat act cac aga   1975
Pro Ser Gln Ser Thr Ser Arg Glu Pro Glu Arg Asn His Thr His Arg
        605                 610                 615

agt ttg ttt tcc gtg gag tct gat gat aca gac aca gaa aat gag aga   2023
Ser Leu Phe Ser Val Glu Ser Asp Asp Thr Asp Thr Glu Asn Glu Arg
    620                 625                 630

aga gat atg gca gga gca tct ggt ggg gtt gca gct cct ttg cct caa   2071
Arg Asp Met Ala Gly Ala Ser Gly Gly Val Ala Ala Pro Leu Pro Gln
635                 640                 645                 650

aaa gtc cct ccc aca acg gca gta gaa gcg aca gta gga gca tgt gca   2119
Lys Val Pro Pro Thr Thr Ala Val Glu Ala Thr Val Gly Ala Cys Ala
                655                 660                 665

agt tcc tca act cag agt acc cga ggt ggc cat gca gat aat gga agg   2167
Ser Ser Ser Thr Gln Ser Thr Arg Gly Gly His Ala Asp Asn Gly Arg
            670                 675                 680

gat gtg aca agt gtg gaa ccc cca agt gtg agt cca gca cgt cac cag   2215
Asp Val Thr Ser Val Glu Pro Pro Ser Val Ser Pro Ala Arg His Gln
        685                 690                 695

ctt aca agt gca ctc agt cgt atg act cag ggg cta cgc tgg gta cgt   2263
Leu Thr Ser Ala Leu Ser Arg Met Thr Gln Gly Leu Arg Trp Val Arg
    700                 705                 710

ttt aca tta gga cga tca agt tcc cta agt cag aac cag agt cct ttg   2311
Phe Thr Leu Gly Arg Ser Ser Ser Leu Ser Gln Asn Gln Ser Pro Leu
715                 720                 725                 730

aga caa ctt gat aat ggg gta agt gga aga gaa gat gat gat gat gtt   2359
Arg Gln Leu Asp Asn Gly Val Ser Gly Arg Glu Asp Asp Asp Asp Val
                735                 740                 745

gaa atg cta att cca att tct gat gga tct tca gac ttt gat gtg aat   2407
Glu Met Leu Ile Pro Ile Ser Asp Gly Ser Ser Asp Phe Asp Val Asn
            750                 755                 760

gac tgc tcc aga cct ctt ctt gat ctt gcc tca gat caa gga cat ggg   2455
Asp Cys Ser Arg Pro Leu Leu Asp Leu Ala Ser Asp Gln Gly Gln Gly
        765                 770                 775

ctt aga caa cca tat aat gca aca att cct gga gta agg cca agt aat   2503
```

```
Leu Arg Gln Pro Tyr Asn Ala Thr Asn Pro Gly Val Arg Pro Ser Asn
    780                 785                 790

cga gat ggc ccc tgt gag cgc tgt ggt att gtc cac act gcc cag ata   2551
Arg Asp Gly Pro Cys Glu Arg Cys Gly Ile Val His Thr Ala Gln Ile
795                 800                 805                 810

cca gac act tgc tta gaa gta aca ctg aaa aac gaa acg agt gat gat   2599
Pro Asp Thr Cys Leu Glu Val Thr Leu Lys Asn Glu Thr Ser Asp Asp
                815                 820                 825

gag gct ttg tta ctt tgt taggtacgaa tcacataagg gagattgtat          2647
Glu Ala Leu Leu Leu Cys
            830

acaagttgga gcaatatcca tttattattt tgtaacttta cagttaaact agttttagtt 2707
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Leu Phe Leu Val Gln Gly Ala His Gly Arg Gly His Arg Glu Asp Phe
                -5                  1                   5

Arg Phe Cys Ser Gln Arg Asn Gln Thr His Arg Ser Ser Leu His Tyr
        10                  15                  20

Lys Pro Thr Pro Asp Leu Arg Ile Ser Ile Glu Asn Ser Glu Glu Ala
    25                  30                  35

Leu Thr Val His Ala Pro Phe Pro Ala Ala His Pro Ala Ser Arg Ser
40                  45                  50                  55
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Phe Pro Asp Pro Arg Gly Leu Tyr His Phe Cys Leu Tyr Trp Asn Arg
60 65 70

His Ala Gly Arg Leu His Leu Leu Tyr Gly Lys Arg Asp Phe Leu Leu
75 80 85

Ser Asp Lys Ala Ser Ser Leu Leu Cys Phe Gln His Gln Glu Glu Ser
90 95 100

Leu Ala Gln Gly Pro Pro Leu Leu Ala Thr Ser Val Thr Ser Trp Trp
105 110 115

Ser Pro Gln Asn Ile Ser Leu Pro Ser Ala Ala Ser Phe Thr Phe Ser
120 125 130 135

Phe His Ser Pro Pro His Thr Ala Ala His Asn Ala Ser Val Asp Met
140 145 150

Cys Glu Leu Lys Arg Asp Leu Gln Leu Leu Ser Gln Phe Leu Lys His
155 160 165

Pro Gln Lys Ala Ser Arg Arg Pro Ser Ala Ala Pro Ala Ser Gln Gln
170 175 180

Leu Gln Ser Leu Glu Ser Lys Leu Thr Ser Val Arg Phe Met Gly Asp
185 190 195

Met Val Ser Phe Glu Glu Asp Arg Ile Asn Ala Thr Val Trp Lys Leu
200 205 210 215

Gln Pro Thr Ala Gly Leu Gln Asp Leu His Ile His Ser Arg Gln Glu
220 225 230

Glu Glu Gln Ser Glu Ile Met Glu Tyr Ser Val Leu Leu Pro Arg Thr
235 240 245

Leu Phe Gln Arg Thr Lys Gly Arg Arg Gly Glu Ala Glu Lys Arg Leu
250 255 260

Leu Leu Val Asp Phe Ser Ser Gln Ala Leu Phe Gln Asp Lys Asn Ser
265 270 275

Ser Gln Val Leu Gly Glu Lys Val Leu Gly Ile Val Val Gln Asn Thr
280 285 290 295

Lys Val Ala Asn Leu Thr Glu Pro Val Val Leu Thr Phe Gln His Gln
300 305 310

Leu Gln Pro Lys Asn Val Thr Leu Gln Cys Val Phe Trp Val Glu Asp
315 320 325

Pro Thr Leu Ser Ser Pro Gly His Trp Ser Ser Ala Gly Cys Glu Thr
330 335 340

Val Arg Arg Glu Thr Gln Thr Ser Cys Phe Cys Asn His Leu Thr Tyr
345 350 355

Phe Ala Val Leu Met Val Ser Ser Val Glu Val Asp Ala Val His Lys
360 365 370 375

His Tyr Leu Ser Leu Leu Ser Tyr Val Gly Cys Val Val Ser Ala Leu
380 385 390

Ala Cys Leu Val Ser Ile Ala Ala Tyr Leu Cys Ser Arg Arg Lys Pro
395 400 405

Arg Asp Tyr Thr Ile Lys Val His Met Asn Leu Leu Leu Ala Val Phe
410 415 420

Leu Leu Asp Thr Ser Phe Leu Leu Ser Glu Pro Val Ala Leu Thr Gly
425 430 435

Ser Glu Ala Gly Cys Arg Ala Ser Ala Ile Phe Leu His Phe Ser Leu
440 445 450 455

Leu Thr Cys Leu Ser Trp Met Gly Leu Glu Gly Tyr Asn Leu Tyr Arg
460 465 470

Leu Val Val Glu Val Phe Gly Thr Tyr Val Pro Gly Tyr Leu Leu Lys
475 480 485

Leu Ser Ala Met Gly Trp Gly Phe Pro Ile Phe Leu Val Thr Leu Val
490 495 500

Ala Leu Val Asp Val Asp Asn Tyr Gly Pro Ile Ile Leu Ala Val His
505 510 515

Arg Thr Pro Glu Gly Val Ile Tyr Pro Ser Met Cys Trp Ile Arg Asp
520 525 530 535

Ser Leu Val Ser Tyr Ile Thr Asn Leu Gly Leu Phe Ser Leu Val Phe
540 545 550

Leu Phe Asn Met Ala Met Leu Ala Thr Met Val Val Gln Ile Leu Arg
555 560 565

Leu Arg Pro His Thr Gln Lys Trp Ser His Val Leu Thr Leu Leu Gly
570 575 580

Leu Ser Leu Val Leu Gly Leu Pro Trp Ala Leu Ile Phe Phe Ser Phe
585 590 595

Ala Ser Gly Thr Phe Gln Leu Val Val Leu Tyr Leu Phe Ser Ile Ile
600 605 610 615

Thr Ser Phe Gln Gly Phe Leu Ile Phe Ile Trp Tyr Trp Ser Met Arg
620 625 630

Leu Gln Ala Arg Gly Gly Pro Ser Pro Leu Lys Ser Asn Ser Asp Ser
635 640 645

Ala Arg Leu Pro Ile Ser Ser Gly Ser Thr Ser Ser Ser Arg Ile
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acacacagga gcagcctcca ctacaaaccc acaccagacc tgcgcatctc catcgagaac  180
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Met Thr Pro Gln
-25

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Ser Leu Leu Gln Thr Thr Leu Phe Leu Leu Ser Leu Leu Phe Leu Val
-20 -15 -10

caa ggt gcc cac ggc agg ggc cac agg gaa gac ttt cgc ttc tgc agc 150
Gln Gly Ala His Gly Arg Gly His Arg Glu Asp Phe Arg Phe Cys Ser

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-5                  1                   5                  10
cag cgg aac cag aca cac agg agc agc ctc cac tac aaa ccc aca cca    198
Gln Arg Asn Gln Thr His Arg Ser Ser Leu His Tyr Lys Pro Thr Pro
            15                  20                  25
gac ctg cgc atc tcc atc gag aac tcc gaa gag gcc ctc aca gtc cat    246
Asp Leu Arg Ile Ser Ile Glu Asn Ser Glu Glu Ala Leu Thr Val His
        30                  35                  40
gcc cct ttc cct gca gcc cac cct gct tcc cga tcc ttc cct gac ccc    294
Ala Pro Phe Pro Ala Ala His Pro Ala Ser Arg Ser Phe Pro Asp Pro
    45                  50                  55
agg ggc ctc tac cac ttc tgc ctc tac tgg aac cga cat gct ggg aga    342
Arg Gly Leu Tyr His Phe Cys Leu Tyr Trp Asn Arg His Ala Gly Arg
60                  65                  70                  75
tta cat ctt ctc tat ggc aag cgt gac ttc ttg ctg agt gac aaa gcc    390
Leu His Leu Leu Tyr Gly Lys Arg Asp Phe Leu Leu Ser Asp Lys Ala
                80                  85                  90
tct agc ctc ctc tgc ttc cag cac cag gag gag agc ctg gct cag ggc    438
Ser Ser Leu Leu Cys Phe Gln His Gln Glu Glu Ser Leu Ala Gln Gly
            95                  100                 105
ccc ccg ctg tta gcc act tct gtc acc tcc tgg tgg agc cct cag aac    486
Pro Pro Leu Leu Ala Thr Ser Val Thr Ser Trp Trp Ser Pro Gln Asn
        110                 115                 120
atc agc ctg ccc agt gcc gcc agc ttc acc ttc tcc ttc cac agt cct    534
Ile Ser Leu Pro Ser Ala Ala Ser Phe Thr Phe Ser Phe His Ser Pro
    125                 130                 135
ccc cac acg gcc gct cac aat gcc tcg gtg gac atg tgc gag ctc aaa    582
Pro His Thr Ala Ala His Asn Ala Ser Val Asp Met Cys Glu Leu Lys
140                 145                 150                 155
agg gac ctc cag ctg ctc agc cag ttc ctg aag cat ccc cag aag gcc    630
Arg Asp Leu Gln Leu Leu Ser Gln Phe Leu Lys His Pro Gln Lys Ala
                160                 165                 170
tca agg agg ccc tcg gct gcc ccc gcc agc cag cag ttg cag agc ctg    678
Ser Arg Arg Pro Ser Ala Ala Pro Ala Ser Gln Gln Leu Gln Ser Leu
            175                 180                 185
gag tcg aaa ctg acc tct gtg aga ttc atg ggg gac atg gtg tcc ttc    726
Glu Ser Lys Leu Thr Ser Val Arg Phe Met Gly Asp Met Val Ser Phe
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                190                 195                 200
gag gag gac cgg atc aac gcc acg gtg tgg aag ctc cag ccc aca gcc   774
Glu Glu Asp Arg Ile Asn Ala Thr Val Trp Lys Leu Gln Pro Thr Ala
    205                 210                 215
ggc ctc cag gac ctg cac atc cac tcc cgg cag gag gag gag cag agc   822
Gly Leu Gln Asp Leu His Ile His Ser Arg Gln Glu Glu Glu Gln Ser
220                 225                 230                 235
gag atc atg gag tac tcg gtg ctg ctg cct cga aca ctc ttc cag agg   870
Glu Ile Met Glu Tyr Ser Val Leu Leu Pro Arg Thr Leu Phe Gln Arg
                240                 245                 250
acg aaa ggc cgg agg ggg gag gct gag aag aga ctc ctc ctg gtg gac   918
Thr Lys Gly Arg Arg Gly Glu Ala Glu Lys Arg Leu Leu Leu Val Asp
            255                 260                 265
ttc agc agc caa gcc ctg ttc cag gac aag aat tcc agc caa gtc ctg   966
Phe Ser Ser Gln Ala Leu Phe Gln Asp Lys Asn Ser Ser Gln Val Leu
        270                 275                 280
ggt gag aag gtc ttg ggg att gtg gta cag aac acc aaa gta gcc aac  1014
Gly Glu Lys Val Leu Gly Ile Val Val Gln Asn Thr Lys Val Ala Asn
    285                 290                 295
ctc acg gag ccc gtg gtg ctc acc ttc cag cac cag cta cag ccg aag  1062
Leu Thr Glu Pro Val Val Leu Thr Phe Gln His Gln Leu Gln Pro Lys
300                 305                 310                 315
aat gtg act ctg caa tgt gtg ttc tgg gtt gaa gac ccc aca ttg agc  1110
Asn Val Thr Leu Gln Cys Val Phe Trp Val Glu Asp Pro Thr Leu Ser
                320                 325                 330
agc ccg ggg cat tgg agc agt gct ggg tgt gag acc gtc agg aga gaa  1158
Ser Pro Gly His Trp Ser Ser Ala Gly Cys Glu Thr Val Arg Arg Glu
            335                 340                 345
acc caa aca tcc tgc ttc tgc aac cac ttg acc tac ttt gca gtg ctg  1206
Thr Gln Thr Ser Cys Phe Cys Asn His Leu Thr Tyr Phe Ala Val Leu
        350                 355                 360
atg gtc tcc tcg gtg gag gtg gac gcc gtg cac aag cac tac ctg agc  1254
Met Val Ser Ser Val Glu Val Asp Ala Val His Lys His Tyr Leu Ser
    365                 370                 375
ctc ctc tcc tac gtg ggc tgt gtc gtc tct gcc ctg gcc tgc ctt gtc  1302
Leu Leu Ser Tyr Val Gly Cys Val Val Ser Ala Leu Ala Cys Leu Val
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380                 385                 390                 395
agc att gcc gcc tac ctc tgc tcc agg agg aaa cct cgg gac tac acc  1350
Ser Ile Ala Ala Tyr Leu Cys Ser Arg Arg Lys Pro Arg Asp Tyr Thr
                400                 405                 410
atc aag gtg cac atg aac ctg ctg ctg gcc gtc ttc ctg ctg gac acg  1398
Ile Lys Val His Met Asn Leu Leu Leu Ala Val Phe Leu Leu Asp Thr
            415                 420                 425
agc ttc ctg ctc agc gag ccg gtg gcc ctg aca ggc tct gag gct ggc  1446
Ser Phe Leu Leu Ser Glu Pro Val Ala Leu Thr Gly Ser Glu Ala Gly
        430                 435                 440
tgc cga gcc agt gcc atc ttc ctg cac ttc tcc ctg ctc acc tgc ctt  1494
Cys Arg Ala Ser Ala Ile Phe Leu His Phe Ser Leu Leu Thr Cys Leu
    445                 450                 455
tcc tgg atg ggc ctc gag ggg tac aac ctc tac cga ctc gtg gtg gag  1542
Ser Trp Met Gly Leu Glu Gly Tyr Asn Leu Tyr Arg Leu Val Val Glu
460                 465                 470                 475
gtc ttt ggc acc tat gtc cct ggc tac cta ctc aag ctg agc gcc atg  1590
Val Phe Gly Thr Tyr Val Pro Gly Tyr Leu Leu Lys Leu Ser Ala Met
                480                 485                 490
ggc tgg ggc ttc ccc atc ttt ctg gtg acg ctg gtg gcc ctg gtg gat  1638
Gly Trp Gly Phe Pro Ile Phe Leu Val Thr Leu Val Ala Leu Val Asp
            495                 500                 505
gtg gac aac tat ggc ccc atc atc ttg gct gtg cat agg act cca gag  1686
Val Asp Asn Tyr Gly Pro Ile Ile Leu Ala Val His Arg Thr Pro Glu
        510                 515                 520
ggc gtc atc tac cct tcc atg tgc tgg atc cgg gac tcc ctg gtc agc  1734
Gly Val Ile Tyr Pro Ser Met Cys Trp Ile Arg Asp Ser Leu Val Ser
    525                 530                 535
tac atc acc aac ctg ggc ctc ttc agc ctg gtg ttt ctg ttc aac atg  1782
Tyr Ile Thr Asn Leu Gly Leu Phe Ser Leu Val Phe Leu Phe Asn Met
540                 545                 550                 555
gcc atg cta gcc acc atg gtg gtg cag atc ctg cgg ctg cgc ccc cac  1830
Ala Met Leu Ala Thr Met Val Val Gln Ile Leu Arg Leu Arg Pro His
                560                 565                 570
acc caa aag tgg tca cat gtg ctg aca ctg ctg ggc ctc agc ctg gtc  1878
Thr Gln Lys Trp Ser His Val Leu Thr Leu Leu Gly Leu Ser Leu Val
```

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                575                 580                 585
ctt ggc ctg ccc tgg gcc ttg atc ttc ttc tcc ttt gct tct ggc acc   1926
Leu Gly Leu Pro Trp Ala Leu Ile Phe Phe Ser Phe Ala Ser Gly Thr
        590                 595                 600
ttc cag ctt gtc gtc ctc tac ctt ttc agc atc atc acc tcc ttc caa   1974
Phe Gln Leu Val Val Leu Tyr Leu Phe Ser Ile Ile Thr Ser Phe Gln
    605                 610                 615
ggc ttc ctc atc ttc atc tgg tac tgg tcc atg cgg ctg cag gcc cgg   2022
Gly Phe Leu Ile Phe Ile Trp Tyr Trp Ser Met Arg Leu Gln Ala Arg
620                 625                 630                 635
ggt ggc ccc tcc cct ctg aag agc aac tca gac agc gcc agg ctc ccc   2070
Gly Gly Pro Ser Pro Leu Lys Ser Asn Ser Asp Ser Ala Arg Leu Pro
                640                 645                 650
atc agc tcg ggc agc acc tcg tcc agc cgc atc taggcctcca gcccacctgc 2123
Ile Ser Ser Gly Ser Thr Ser Ser Ser Arg Ile
            655                 660
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Cys	Glu	Lys	Val	Tyr	Ser	Asp	Cys	Lys	Lys	Leu	Ile	Asp	Thr	Phe	Gly
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Arg	His	Leu	Lys	Thr	Ser	Gly	Gly	Gln	Gly	Tyr	Lys	Phe	Leu	Gly	Ile
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Cys Ala Thr Leu Phe Thr Phe Leu Thr Phe Leu Ile Asp Val Arg Arg
        195                 200                 205
Phe Arg Tyr Pro Glu Arg Pro Ile Ile Tyr Tyr Ser Val Cys Tyr Ser
    210                 215                 220
Ile Val Ser Leu Met Tyr Phe Ile Gly Phe Leu Leu Gly Asp Ser Thr
225                 230                 235                 240
Ala Cys Asn Lys Ala Asp Glu Lys Leu Glu Leu Gly Asn Thr Val Val
                245                 250                 255
Leu Asp Ser Gln Asn Lys Ala Cys Thr Val Leu Phe Met Leu Leu Tyr
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Phe Phe Thr Met Ala Gly Thr Val Trp Trp Val Ile Leu Thr Ile Thr
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Trp Phe Leu Ala Ala Gly Arg Lys Trp Ser Cys Glu Ala Ile Glu Gln
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Lys Ala Val Trp Phe His Ala Val Ala Trp Gly Thr Pro Gly Phe Leu
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Thr Val Met Leu Leu Ala Met Asn Lys Val Glu Gly Asp Asn Ile Ser
                325                 330                 335
Gly Val Cys Phe Val Gly Leu Tyr Asp Leu Asp Ala Ser Arg Tyr Phe
            340                 345                 350
Val Leu Leu Pro Leu Cys Leu Cys Val Phe Val Gly Leu Ser Leu Leu
        355                 360                 365
Leu Ala Gly Ile Ile Ser Leu Asn His Val Arg Gln Val Ile Gln His
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Asp Gly Arg Asn Gln Glu Lys Leu Lys Lys Phe Met Ile Arg Ile Gly
385                 390                 395                 400
Val Phe Ser Gly Leu Tyr Leu Val Pro Leu Val Thr Leu Leu Gly Cys
                405                 410                 415
Tyr Val Tyr Glu Gln Val Asn Arg Ile Thr Trp Glu Ile Thr Trp Val
            420                 425                 430
Ser Asp His Cys Arg Gln Tyr His Ile Pro Cys Pro Tyr Gln Ala Lys
        435                 440                 445
Ala Lys Ala Arg Pro Glu Leu Ala Leu Phe Met Ile Lys Tyr Leu Met
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Thr Cys Thr Glu Trp Ala Gly Phe Phe Lys Arg Asn Arg Lys Arg Asp
485 490 495

Pro Ile Ser Glu Ser Arg Arg Val Leu Gln Glu Ser Cys Glu Phe Phe
500 505 510

Leu Lys His Asn Ser Lys Val Lys His Lys Lys Lys His Tyr Lys Pro
515 520 525

Ser Ser His Lys Leu Lys Val Ile Ser Lys Ser Met Gly Thr Ser Thr
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Gly Ala Thr Ala Asn His Gly Thr Ser Ala Val Ala Ile Thr Ser His
545 550 555 560

Asp Tyr Leu Gly Gln Glu Thr Leu Thr Glu Ile Gln Thr Ser Pro Glu
565 570 575

Thr Ser Met Arg Glu Val Lys Ala Asp Gly Ala Ser Thr Pro Arg Leu
580 585 590

Arg Glu Gln Asp Cys Gly Glu Pro Ala Ser Pro Ala Ala Ser Ile Ser
595 600 605

Arg Leu Ser Gly Glu Gln Val Asp Gly Lys Gly Gln Ala Gly Ser Val
610 615 620

Ser Glu Ser Ala Arg Ser Glu Gly Arg Ile Ser Pro Lys Ser Asp Ile
625 630 635 640

Thr Asp Thr Gly Leu Ala Gln Ser Asn Asn Leu Gln Val Pro Ser Ser
645 650 655

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<400> 78

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      -16 -15                 -10                 -5

aga ggg cac agt ctc ttc acc tgt gaa cca att act gtt ccc aga tgt     95
Arg Gly His Ser Leu Phe Thr Cys Glu Pro Ile Thr Val Pro Arg Cys
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atg aaa atg gcc tac aac atg acg ttt ttc cct aat ctg atg ggt cat    143
Met Lys Met Ala Tyr Asn Met Thr Phe Phe Pro Asn Leu Met Gly His
 15                  20                  25                  30

tat gac cag agt att gcc gcg gtg gaa atg gag cat ttt ctt cct ctc    191
Tyr Asp Gln Ser Ile Ala Ala Val Glu Met Glu His Phe Leu Pro Leu
                 35                  40                  45

gca aat ctg gaa tgt tca cca aac att gaa act ttc ctc tgc aaa gca    239
Ala Asn Leu Glu Cys Ser Pro Asn Ile Glu Thr Phe Leu Cys Lys Ala
             50                  55                  60

ttt gta cca acc tgc ata gaa caa att cat gtg gtt cca cct tgt cgt    287
Phe Val Pro Thr Cys Ile Glu Gln Ile His Val Val Pro Pro Cys Arg
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aaa ctt tgt gag aaa gta tat tct gat tgc aaa aaa tta att gac act   335
Lys Leu Cys Glu Lys Val Tyr Ser Asp Cys Lys Lys Leu Ile Asp Thr
     80                  85                  90
ttt ggg atc cga tgg cct gag gag ctt gaa tgt gac aga tta caa tac   383
Phe Gly Ile Arg Trp Pro Glu Glu Leu Glu Cys Asp Arg Leu Gln Tyr
 95                  100                 105                 110
tgt gat gag act gtt cct gta act ttt gat cca cac aca gaa ttt ctt   431
Cys Asp Glu Thr Val Pro Val Thr Phe Asp Pro His Thr Glu Phe Leu
                115                 120                 125
ggt cct cag aag aaa aca gaa caa gtc caa aga gac att gga ttt tgg   479
Gly Pro Gln Lys Lys Thr Glu Gln Val Gln Arg Asp Ile Gly Phe Trp
            130                 135                 140
tgt cca agg cat ctt aag act tct ggg gga caa gga tat aag ttt ctg   527
Cys Pro Arg His Leu Lys Thr Ser Gly Gly Gln Gly Tyr Lys Phe Leu
        145                 150                 155
gga att gac cag tgt gcg cct cca tgc ccc aac atg tat ttt aaa agt   575
Gly Ile Asp Gln Cys Ala Pro Pro Cys Pro Asn Met Tyr Phe Lys Ser
    160                 165                 170
gat gag cta gag ttt gca aaa agt ttt att gga aca gtt tca ata ttt   623
Asp Glu Leu Glu Phe Ala Lys Ser Phe Ile Gly Thr Val Ser Ile Phe
175                 180                 185                 190
tgt ctt tgt gca act ctg ttc aca ttc ctt act ttt tta att gat gtt   671
Cys Leu Cys Ala Thr Leu Phe Thr Phe Leu Thr Phe Leu Ile Asp Val
                195                 200                 205
aga aga ttc aga tac cca gag aga cca att ata tat tac tct gtc tgt   719
Arg Arg Phe Arg Tyr Pro Glu Arg Pro Ile Ile Tyr Tyr Ser Val Cys
            210                 215                 220

tac agc att gta tct ctt atg tac ttc att gga ttt ttg cta ggc gat   767
Tyr Ser Ile Val Ser Leu Met Tyr Phe Ile Gly Phe Leu Leu Gly Asp
        225                 230                 235
agc aca gcc tgc aat aag gca gat gag aag cta gaa ctt ggt aac act   815
Ser Thr Ala Cys Asn Lys Ala Asp Glu Lys Leu Glu Leu Gly Asn Thr
    240                 245                 250
gtt gtc cta gac tct caa aat aag gct tgc acc gtt ttg ttc atg ctt   863
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Val Val Leu Asp Ser Gln Asn Lys Ala Cys Thr Val Leu Phe Met Leu
255                 260                 265                 270
ttg tat ttt ttc aca atg gct ggc act gtg tgg tgg gtg att ctt acc   911
Leu Tyr Phe Phe Thr Met Ala Gly Thr Val Trp Trp Val Ile Leu Thr
                275                 280                 285
att act tgg ttc tta gct gca gga aga aaa tgg agt tgt gaa gcc atc   959
Ile Thr Trp Phe Leu Ala Ala Gly Arg Lys Trp Ser Cys Glu Ala Ile
            290                 295                 300
gag caa aaa gca gtg tgg ttt cat gct gtt gca tgg gga aca cca ggt  1007
Glu Gln Lys Ala Val Trp Phe His Ala Val Ala Trp Gly Thr Pro Gly
        305                 310                 315
ttc ctg act gtt atg ctt ctt gct atg aac aaa gtt gaa gga gac aac  1055
Phe Leu Thr Val Met Leu Leu Ala Met Asn Lys Val Glu Gly Asp Asn
    320                 325                 330
att agt gga gtt tgc ttt gtt ggc ctt tat gac ctg gat gct tct cgc  1103
Ile Ser Gly Val Cys Phe Val Gly Leu Tyr Asp Leu Asp Ala Ser Arg
335                 340                 345                 350
tac ttt gta ctc ttg cca ctg tgc ctt tgt gtg ttt gtt ggg ctc tct  1151
Tyr Phe Val Leu Leu Pro Leu Cys Leu Cys Val Phe Val Gly Leu Ser
                355                 360                 365
ctt ctt tta gct ggc att att tcc tta aat cat gtt cga caa gtc ata  1199
Leu Leu Leu Ala Gly Ile Ile Ser Leu Asn His Val Arg Gln Val Ile
            370                 375                 380
caa cat gat ggc cgg aac caa gaa aaa cta aag aaa ttt atg att cga  1247
Gln His Asp Gly Arg Asn Gln Glu Lys Leu Lys Lys Phe Met Ile Arg
        385                 390                 395
att gga gtc ttc agc ggc ttg tat ctt gtg cca tta gtg aca ctt ctc  1295
Ile Gly Val Phe Ser Gly Leu Tyr Leu Val Pro Leu Val Thr Leu Leu
    400                 405                 410
gga tgt tac gtc tat gag caa gtg aac agg att acc tgg gag ata act  1343
Gly Cys Tyr Val Tyr Glu Gln Val Asn Arg Ile Thr Trp Glu Ile Thr
415                 420                 425                 430
tgg gtc tct gat cat tgt cgt cag tac cat atc cca tgt cct tat cag  1391
Trp Val Ser Asp His Cys Arg Gln Tyr His Ile Pro Cys Pro Tyr Gln
                435                 440                 445
gca aaa gca aat gct cga cca gaa ttg gct tta ttt atg ata aat tac  1439
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Ala Lys Ala Lys Ala Arg Pro Glu Leu Ala Leu Phe Met Ile Lys Tyr
          450                 455                 460

ctg atg aca tta att gtt ggc atc tct gct gtc ttc tgg gtt gga agc  1487
Leu Met Thr Leu Ile Val Gly Ile Ser Ala Val Phe Trp Val Gly Ser
      465                 470                 475

aaa aag aca tgc aca gaa tgg gct ggg ttt ttt aaa cga aat cgc aag  1535
Lys Lys Thr Cys Thr Glu Trp Ala Gly Phe Phe Lys Arg Asn Arg Lys
  480                 485                 490

aga gat cca atc agt gaa agt cga aga gta cta cag gaa tca tgt gag  1583
Arg Asp Pro Ile Ser Glu Ser Arg Arg Val Leu Gln Glu Ser Cys Glu
495                 500                 505                 510

ttt ttc tta aag cac aat tct aaa gtt aaa cac aaa aag aag cac tat  1631
Phe Phe Leu Lys His Asn Ser Lys Val Lys His Lys Lys Lys His Tyr
                515                 520                 525

aaa cca agt tca cac aag ctg aag gtc att tcc aaa tcc atg gga acc  1679
Lys Pro Ser Ser His Lys Leu Lys Val Ile Ser Lys Ser Met Gly Thr
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agc aca gga gct aca gca aat cat ggc act tct gca gta gca att act  1727
Ser Thr Gly Ala Thr Ala Asn His Gly Thr Ser Ala Val Ala Ile Thr
      545                 550                 555

agc cat gat tac cta gga caa gaa act ttg aca gaa atc caa acc tca  1775
Ser His Asp Tyr Leu Gly Gln Glu Thr Leu Thr Glu Ile Gln Thr Ser
  560                 565                 570

cca gaa aca tca atg aga gag gtg aaa gcg gac gga gct agc acc ccc  1823
Pro Glu Thr Ser Met Arg Glu Val Lys Ala Asp Gly Ala Ser Thr Pro
575                 580                 585                 590

agg tta aga gaa cag gac tgt ggt gaa cct gcc tcg cca gca gca tcc  1871
Arg Leu Arg Glu Gln Asp Cys Gly Glu Pro Ala Ser Pro Ala Ala Ser
                595                 600                 605

atc tcc aga ctc tct ggg gaa cag gtc gac ggg aag ggc cag gca ggc  1919
Ile Ser Arg Leu Ser Gly Glu Gln Val Asp Gly Lys Gly Gln Ala Gly
          610                 615                 620

agt gta tct gaa agt gcg cgg agt gaa gga agg att agt cca aag agt  1967
Ser Val Ser Glu Ser Ala Arg Ser Glu Gly Arg Ile Ser Pro Lys Ser
      625                 630                 635

gat att act gac act ggc ctg gca cag agc aac aat ttg cag gtc ccc  2015
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Asp Ile Thr Asp Thr Gly Leu Ala Gln Ser Asn Asn Leu Gln Val Pro
640 645 650

agt tct tca gaa cca agc agc ctc aaa ggt tcc aca tct ctg ctt gtt 2063
Ser Ser Ser Glu Pro Ser Ser Leu Lys Gly Ser Thr Ser Leu Leu Val
655 660 665 670

cac ccg gtt tca gga gtg aga aaa gag cag gga ggt ggt tgt cat tca 2111
His Pro Val Ser Gly Val Arg Lys Glu Gln Gly Gly Gly Cys His Ser
675 680 685

gat act tgaagaacat tttctctcgt tactcagaag caaatttgtg ttacactgga 2167
Asp Thr

agtgacctat gcactgtttt gtaagaatca ctgttacgtt cttcttttgc acttaaagtt 2227
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Ser Gly Glu Lys Asp Val Ser Pro Asp Leu Ser Cys Ala Asp Glu Ile
                    35                  40                  45
Ser Glu Cys Tyr His Lys Leu Asp Ser Leu Thr Tyr Lys Ile Asp Glu
                50                  55                  60
Cys Glu Lys Lys Lys Arg Glu Asp Tyr Glu Ser Gln Ser Asn Pro Val
            65                  70                  75
Phe Arg Arg Tyr Leu Asn Lys Ile Leu Ile Glu Ala Gly Lys Leu Gly
        80                  85                  90
Leu Pro Asp Glu Asn Lys Gly Asp Met His Tyr Asp Ala Glu Ile Ile
 95                  100                 105                 110
Leu Lys Arg Glu Thr Leu Leu Glu Ile Gln Lys Phe Leu Asn Gly Glu
                    115                 120                 125

Asp Trp Lys Pro Gly Ala Leu Asp Asp Ala Leu Ser Asp Ile Leu Ile
                130                 135                 140
Asn Phe Lys Phe His Asp Phe Glu Thr Trp Lys Trp Arg Phe Glu Asp
            145                 150                 155
Ser Phe Gly Val Asp Pro Tyr Asn Val Leu Met Val Leu Leu Cys Leu
        160                 165                 170
Leu Cys Ile Val Val Leu Val Ala Thr Glu Leu Trp Thr Tyr Val Arg
175                 180                 185                 190
Trp Tyr Thr Gln Leu Arg Arg Val Leu Ile Ile Ser Phe Leu Phe Ser
                    195                 200                 205
Leu Gly Trp Asn Trp Met Tyr Leu Tyr Lys Leu Ala Phe Ala Gln His
                210                 215                 220
Gln Ala Glu Val Ala Lys Met Glu Pro Leu Asn Asn Val Cys Ala Lys
            225                 230                 235
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Lys Met Asp Trp Thr Gly Ser Ile Trp Glu Trp Phe Arg Ser Ser Trp
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Thr Tyr Lys Asp Asp Pro Cys Gln Lys Tyr Tyr Glu Leu Leu Leu Val
255 260 265 270
Asn Pro Ile Trp Leu Val Pro Pro Thr Lys Ala Leu Ala Val Thr Phe
275 280 285
Thr Thr Phe Val Thr Glu Pro Leu Lys His Ile Gly Lys Gly Thr Gly
290 295 300
Glu Phe Ile Lys Ala Leu Met Lys Glu Ile Pro Ala Leu Leu His Leu
305 310 315
Pro Val Leu Ile Ile Met Ala Leu Ala Ile Leu Ser Phe Cys Tyr Gly
320 325 330
Ala Gly Lys Ser Val His Val Leu Arg His Ile Gly Gly Pro Glu Ser
335 340 345 350
Glu Pro Pro Gln Ala Leu Arg Pro Arg Asp Arg Arg Arg Gln Glu Glu
355 360 365
Ile Asp Tyr Arg Pro Asp Gly Gly Ala Gly Asp Ala Asp Phe His Tyr
370 375 380
Arg Gly Gln Met Gly Pro Thr Glu Gln Gly Pro Tyr Ala Lys Thr Tyr
385 390 395
Glu Gly Arg Arg Glu Ile Leu Arg Glu Arg Asp Val Asp Leu Arg Phe
400 405 410
Gln Thr Gly Asn Lys Ser Pro Glu Val Leu Arg Ala Phe Asp Val Pro
415 420 425 430
Asp Ala Glu Ala Arg Glu His Pro Thr Val Val Pro Ser His Lys Ser
435 440 445
Pro Val Leu Asp Thr Lys Pro Lys Glu Thr Gly Gly Ile Leu Gly Glu
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Gln Ala Lys Tyr Gly Ile Ser Gly Glu Lys Asp Val Ser Pro Asp Leu
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Glu Ala Gly Lys Leu Gly Leu Pro Asp Glu Asn Lys Gly Asp Met His
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Tyr Asp Ala Glu Ile Ile Leu Lys Arg Glu Thr Leu Leu Glu Ile Gln
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aag ttt ctc aat gga gaa gac tgg aaa cca ggt gcc ttg gat gat gca   543
Lys Phe Leu Asn Gly Glu Asp Trp Lys Pro Gly Ala Leu Asp Asp Ala
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cta agt gat att tta att aat ttt aag ttt cat gat ttt gaa aca tgg   591
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aag tgg cga ttc gaa gat tcc ttt gga gtg gat cca tat aat gtg tta   639
Lys Trp Arg Phe Glu Asp Ser Phe Gly Val Asp Pro Tyr Asn Val Leu
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Met Val Leu Leu Cys Leu Leu Cys Ile Val Val Leu Val Ala Thr Glu
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Leu Trp Thr Tyr Val Arg Trp Tyr Thr Gln Leu Arg Arg Val Leu Ile
185                 190                 195                 200

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Ile Ser Phe Leu Phe Ser Leu Gly Trp Asn Trp Met Tyr Leu Tyr Lys
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Leu Ala Phe Ala Gln His Gln Ala Glu Val Ala Lys Met Glu Pro Leu
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Asn Asn Val Cys Ala Lys Lys Met Asp Trp Thr Gly Ser Ile Trp Glu
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Tyr Glu Leu Leu Leu Val Asn Pro Ile Trp Leu Val Pro Pro Thr Lys
265                 270                 275                 280

gca ctt gca gtt aca ttc acc aca ttt gta acg gag cca ttg aag cat   1023
Ala Leu Ala Val Thr Phe Thr Thr Phe Val Thr Glu Pro Leu Lys His
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cca gcg ctg ctt cat ctt cca gtg ctg ata att atg gca tta gcc atc   1119
Pro Ala Leu Leu His Leu Pro Val Leu Ile Ile Met Ala Leu Ala Ile
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Arg Arg Arg Gln Glu Glu Ile Asp Tyr Arg Pro Asp Gly Gly Ala Gly
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Claims

1. A substantially purified form of the polypeptide comprising the amino acid sequence shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79, homologue thereof, fragment thereof or homologue of the fragment.

2. A polypeptide according to claim 1 comprising the amino acid sequence shown in SEQ ID NOS. 1, 4, 7, 10, 13, 16, 19, 22, 25, 28, 31, 34, 37, 40, 43, 46, 49, 52, 55, 58, 61, 64, 67, 70, 73, 76 or 79.

3. A cDNA encoding the polypeptide according to claim 1.

4. A cDNA according to claim 3 comprising the nucleotide sequence shown in SEQ ID NOS. 2, 5, 8, 11, 14, 17, 20, 23, 26, 29, 32, 35, 38, 41, 44, 47, 50, 53, 56, 59, 62, 65, 68, 71, 74, 77 or 80, or a fragment cDNA selectively hybridized to the cDNA.

5. A cDNA according to claim 3 comprising the nucleotide sequence shown in SEQ ID NOS. 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78 or 81, or a fragment cDNA selectively hybridized to the cDNA.

6. A replication or expression vector carrying the cDNA according to claims 3 to 5.

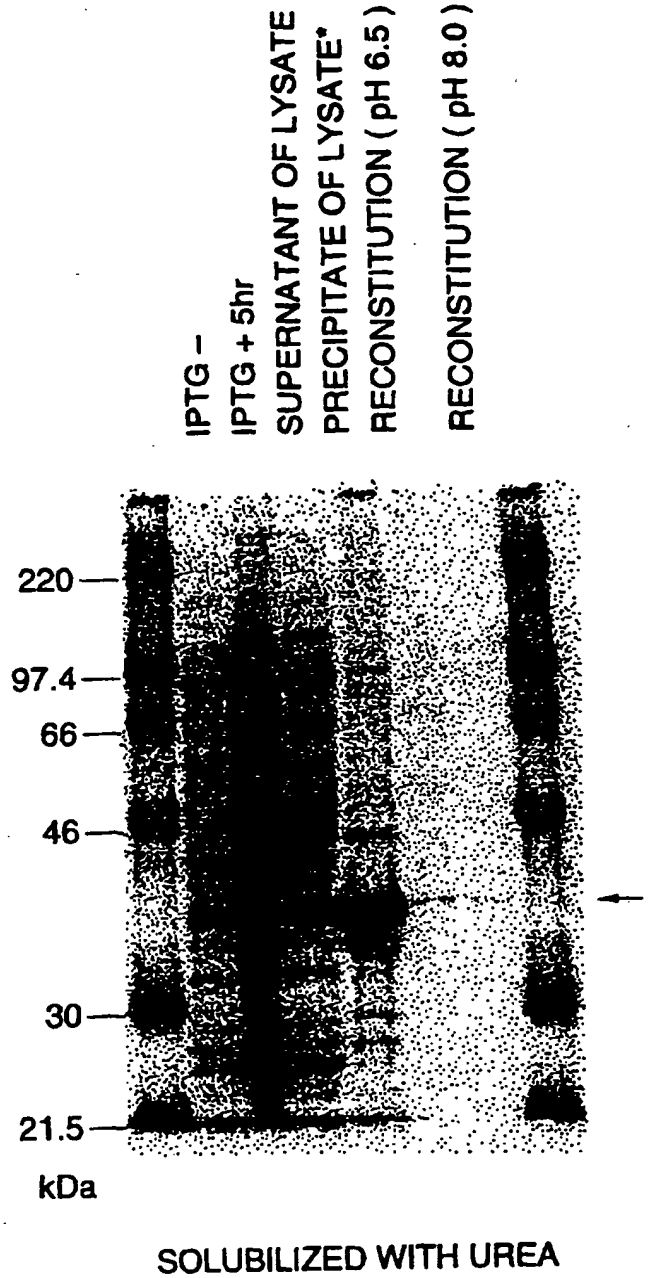
7. A host cell transformed with the replication or expression vector according to claim 6.

8. A method for producing the polypeptide according to claim 1 or 2 which comprises culturing a host cell according to claim 7 under a condition effective to express the polypeptide according to claim 1 or 2.

9. A monoclonal or polyclonal antibody against the polypeptide according to claim 1 or 2.

10. A pharmaceutical composition containing the polypeptide according to claim 1 or 2 or the antibody according to claim 9, in association with pharmaceutically acceptable diluent and/or carrier.

FIG. 1


IPTG –
IPTG + 5hr
SUPERNATANT OF LYSATE
PRECIPITATE OF LYSATE'
RECONSTITUTION (pH 6.5)
RECONSTITUTION (pH 8.0)
220
97.4
66
46
30
21.5
kDa
SOLUBILIZED WITH UREA

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/04514

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07K14/47, C12N15/12, C12P21/02, C12P21/08, C07K16/18, A61K39/395, A61K38/17, A61K48/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07K14/47, C12N15/12, C12P21/02, C12P21/08, C07K16/18, A61K39/395, A61K38/17, A61K48/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
SwissPort/PIR/GeneSeq, Genbank/EMBL/DDBJ/GeneSeq, WPI (DIALOG), BIOSIS (DIALOG)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Okamura, N. et al., "Direct evidence for the elevated synthesis and secretion of procathepsin L in the distal caput epididy-mis of boar", Biochim Biophys Acta (1995) vol. 1245, No. 2 p.221-226	1-10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January, 1999 (27. 01. 99)	2 February, 1999 (02. 02. 99)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/04514

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1 to 10, provided the internal search report covers, among the inventions related to these claims, only those inventions which relate to a polypeptide comprising the amino acid sequence represented by SEQ ID NO:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/04514

Continuation of Box No. II of continuation of first sheet (1)

1 and a process for producing the same, a cDNA encoding the same, a replication or expression vector comprising the cDNA, a host cell transformed with the vector, a monoclonal or polyclonal antibody against the polypeptide, and a pharmaceutical composition containing the polypeptide and/or the antibody.

Concerning claims 1 to 10

According to the disclosure in the description of the present invention, "polypeptides respectively comprising the amino acid sequence represented by SEQ ID NO: 1, 4, 7, ... 76 or 79 or polypeptides respectively comprising the homolog, fragment or homolog of the fragment of the above polypeptides" as set forth in claim 1 and "the polypeptides as set forth in claim 1 respectively comprising the amino acid sequence represented by SEQ ID NO:1, 4, 7, ... 76 or 79" as set forth in claim 2 are assumed to be polypeptides having 27 kinds of utterly different functions and constitutions, except for the common feature that they are secretory or membrane proteins, and a plurality of such secretory or membrane proteins are well known. Therefore, the fact of being secretory or membrane proteins is not considered special technical features in common among these 27 kinds of polypeptides.

Such being the case, each of the above claims is considered to describe 27 inventions. When the unity of invention is taken into account concerning the 27 inventions based on the above consideration, these polypeptides are considered neither those attaining common purposes nor those having common principal parts, and thus it does not appear that there is a technical relationship among these 27 inventions involving one or more of the same or corresponding special technical features. As a result, claims 1 and 2 are not considered fulfilling the requirement of unity of invention.

For the same reason, the requirement of unity of invention is not considered fulfilled as regards the cDNA as set forth in claims 3, 4 and 5, the replication or expression vector in claim 6, the host cell in claim 7, the process for producing a polypeptide in claim 8, the monoclonal or polyclonal antibody in claim 9, and the pharmaceutical composition in claim 10.

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